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
Avapritinib (new therapeutic indication: indolent systemic mastocytosis (ISM))

of 20 June 2024

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 active ingredient avapritinib (Ayvakyt) was listed for the first time on 1 November 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 11 December 2023, avapritinib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 20 December 2023, the pharmaceutical company has submitted a dossier in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication) in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient avapritinib with the new therapeutic indication:

"Treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment".

Avapritinib for the treatment of indolent systemic mastocytosis (ISM) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed 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 April 2024 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted 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 G23-32) and the statements made in the written statement and oral hearing procedure, as well as the amendment to the benefit assessment drawn up by the G-BA.

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 avapritinib.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Avapritinib (Ayvakyt) in accordance with the product information

AYVAKYT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment**.**

Therapeutic indication of the resolution (resolution of 20 June 2024):

See new therapeutic indication according to marketing authorisation.

2.1.2 Extent of the additional benefit and significance of the evidence

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

Adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment

Indication of a minor additional benefit

Justification:

For the benefit assessment of avapritinib for the treatment of adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment, the pharmaceutical company is presenting data from the pivotal PIONEER study.

PIONEER is an ongoing phase II study that is divided into three parts. In the first part of the study, the avapritinib dose was determined. The second part of the study comprises the double-blind, randomised study phase in which avapritinib was compared with placebo, in each case in combination with best supportive care (BSC) over 24 weeks. The third part of the study examines long-term safety. The study is being conducted at 42 study sites in Europe and North America.

The second part of the study is used for the benefit assessment. In the double-blind, randomised study phase, a total of 212 patients aged between 18 and 79 years with a confirmed diagnosis of indolent systemic mastocytosis who had a total symptom score (TSS) ≥ 28 on the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) despite symptomatic treatment were enrolled in the study. The patients enrolled were randomised in a 2:1 ratio to the two study arms (avapritinib: N = 141; placebo: N = 71). Randomisation was stratified by serum tryptase level (< 20 ng/ml vs ≥ 20 ng/ml).

The pharmaceutical company submits the data cut-off from 23.06.2022, which includes the fully completed second part of the study. The benefit assessment is based on this data cut-off.

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

About the analysis population

In the dossier, the pharmaceutical company only prepares the results of the per protocol (PP) analysis population. Compared to the intention-to-treat (ITT) analysis population, all patients with an ISM-SAF TSS score < 28 at baseline were excluded from the PP analysis population. Although a TSS score ≥ 28 is an inclusion criterion that was met at the time of screening, 18 patients (12.8%) in the avapritinib arm and 4 patients (5.6%) in the placebo arm of the ITT population had a TSS score < 28 at baseline. Overall, the PP population comprises almost 90% of the ITT population.

The pharmaceutical company submits analyses for the ITT population as part of the written statement procedure.

Analyses of the PP population represent an interruption in randomisation and are therefore inherently associated with an increased risk of bias. For this reason, the ITT population is used for the benefit assessment, as this was pre-specified in the statistical analysis plan and includes all randomised patients.

Mortality

No deaths occurred in the second part of the PIONEER study.

Morbidity

Symptomatology measured using the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF)

The ISM-SAF is a patient-reported endpoint to assess the symptoms of patients with ISM. The ISM-SAF consists of 11 items, which are rated according to severity on an 11-point scale (0 - 10), as well as an item to determine the frequency of diarrhoea.

The items surveyed by the ISM-SAF are abdominal pain, nausea, diarrhoea, spots on the skin, itching, hot flushes, bone pain, fatigue, dizziness, drowsiness and headaches.

The ISM-SAF total symptom score (TSS) can reach values between 0 and 110, with a higher value indicating more pronounced symptomatology. In addition, domain scores for gastrointestinal (abdominal pain, nausea and diarrhoea), cutaneous (spots on the skin, itching and hot flushes) and neurocognitive (dizziness, brain fog and headaches) symptoms are formed, reaching values between 0 and 30.

The analyses on the ITT population subsequently submitted by the pharmaceutical company in the written statement procedure are used for the benefit assessment. Responder analyses are available on the percentage of subjects with an improvement of at least 15% of the scale range at week 24 as well as analyses of the continuous data on the individual (most severe) lead symptom and (most severe) lead domain/ lead symptom cluster.

The responder analysis of the ISM-SAF shows a statistically significant difference in the skin domain symptom score in favour of avapritinib. The ISM-SAF total symptom score and the domains "gastrointestinal symptoms" and "neurocognitive symptom cluster" showed no statistically significant differences between the treatment arms.

In the analysis of the individually determined lead symptom and the lead domain, mean differences and Hedges' g are presented by the pharmaceutical company. Both the lead symptom and the lead domain showed a significant improvement in the mean difference in the avapritinib arm. The 95% confidence interval of the standardised mean difference

(Hedges' g) of the lead domain is outside the irrelevance threshold (-0.2 to 0.2), so that the effect is classified as clinically relevant. This is not the case for the lead symptom, so it cannot be concluded with sufficient certainty that the observed effect is clinically relevant for the lead symptom.

Patient Global Impression of Symptom Severity (PGIS)/ Patient Global Impression of Change (PGIC)

The PGIS is used in the PIONEER study in addition to the ISM-SAF to survey symptomatology. The PGIS consists of a question asking patients to rate the severity of their symptoms on a 5-point scale ("no symptoms", "minimal", "moderate", "severe" and "very severe").

The responder analyses on the ITT population subsequently submitted by the pharmaceutical company in the written statement procedure are used for the benefit assessment.

There was a statistically significant advantage of avapritinib in the PGIS.

The PGIC is used to survey changes in the health status. The PGIC used in the PIONEER study does not correspond to the conventional version of the instrument. The PGIC used in the study consisted of two single-item scales.

The first item was a 7-point scale to assess general improvement. Due to the similarity of the response options and the fact that one response option neither included change nor deterioration and it is therefore not clear in how many patients deterioration occurred, the first item of the PGIC is not used for the benefit assessment.

The second item of the PGIC used comprised the extent of change since the start of treatment, which was determined using a visual analogue scale. On the 11-point scale, 0 corresponded to a significant improvement, 5 to no change and 10 to a significant deterioration.

The second item is favoured over the first item because it is easier to distinguish between an improvement or deterioration of the general condition, and is used for the benefit assessment.

There was no statistically significant difference between the two treatment arms for the PGIC.

Health status (EQ-5D VAS) (visual analogue scale of the European Quality of Life Questionnaire – 5 Dimensions)

Health status was surveyed in the PIONEER study using the EQ-5D VAS. Using EQ-5D VAS, the study participants rate their health status themselves on a scale from 0 (worst perceivable health status) to 100 (best perceivable health status).

The responder analyses on the ITT population subsequently submitted in the written statement procedure are used for the benefit assessment. These refer to the percentage of patients with an improvement of at least 15% of the scale range at week 24.

The responder analysis of the EQ-5D VAS shows a statistically significant effect in favour of avapritinib.

Conclusion on the morbidity endpoint category

An overall advantage of avapritinib can be derived from the overall analysis of the symptomatology and health status endpoints.

The responder analysis in the ISM-SAF endpoint shows an advantage with regard to skin symptomatology. However, the responder analysis shows no improvements in the other domains or the total score.

During the oral hearing, the clinicians and patient representatives pointed out the very heterogeneous clinical picture of indolent systemic mastocytosis. The majority of patients are affected by a skin infestation, although this is only observed as a severe manifestation in some ISM patients. In addition, other symptoms in the gastrointestinal and neurocognitive areas are of great importance for patients and lead to considerable impairment.

The patient-individual improvement in symptomatology is assessed by evaluating the individual lead symptom and the lead domain of the ISM-SAF. However, only the lead domain has an effect magnitude of clinical relevance.

The PGIS and the EQ-5D VAS were surveyed as further endpoints in the morbidity category; a significant advantage of avapritinib was derived for both endpoints.

Health-related quality of life

In the PIONEER study, data on health-related quality of life was collected using the Short-Form 12 Health Survey Version 2 (SF-12) and the Mastocytosis Quality of Life Questionnaire (MC-QoL).

Short Form-12 Health Survey Version 2 (SF-12)

The SF-12 is a shortened version of the SF-36 and comprises the 8 domains of the SF-36, whereby the number of items per domain was reduced. As with the SF-36, two summary scores – the Mental Component Summary (MCS) and the Physical Component Summary (PCS) – can be formed for the SF-12. The revised version 2 of the SF-12 was used in the study.

The responder analyses on the ITT population subsequently submitted in the written statement procedure are used for the benefit assessment. These refer to the percentage of patients with an improvement of ≥ 9.1 points in the PCS and an improvement of ≥ 8.5 points in the MCS at week 24.

The responder analysis of the SF-12 shows a statistically significant effect in favour of avapritinib for the PCS. There was no significant difference for the MCS.

Mastocytosis Quality of Life Questionnaire (MC-QoL)

The disease-specific Mastocytosis Quality of Life Questionnaire (MC-QoL) was also used to survey quality of life. The questionnaire comprises 27 items from the domains of symptoms, social life/ functioning, emotions and skin. Patients answer the items relating to the last 2 weeks on a 5-point Likert scale.

The total and domain scores are calculated by adding them together and then linearly transforming them on a scale from 0 to 100. A higher score reflects a higher impairment of quality of life.

The analyses of the continuous data with Hedges' g for the ITT population subsequently submitted in the written statement procedure are used for the benefit assessment.

Avapritinib showed a statistically significant advantage for the mean differences in the total and domain scores. However, the 95% confidence interval of the standardised mean difference (Hedges' g) is within the irrelevance threshold (-0.2 to 0.2), so that it cannot be concluded with sufficient certainty that the observed effect is clinically relevant.

Conclusion on the health-related quality of life endpoint category

Results of the SF-12 and the MC-QoL are available for the endpoint category of health-related quality of life. The physical component summary of the SF-12 endpoint shows an advantage of avapritinib. For the present differences in MC-QoL, it cannot be concluded with sufficient certainty that the observed effect is clinically relevant.

Side effects

Adverse events (AEs) in total

AEs occurred in almost all study participants. The results were only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AE

There were no statistically significant differences between treatment arms for SAEs, severe AEs (CTCAE grade ≥ 3), and therapy discontinuations due to AE.

Specific AEs

At SOC and PT level, there are no suitable analyses including effect estimators for SAEs and severe AEs with CTCAE grade ≥ 3.

With regard to AEs of special interest, there was a significant disadvantage for the occurrence of oedema in the avapritinib arm. However, severe oedema (CTCAE grade 3 or higher) did not occur.

Overall assessment

For the assessment of the additional benefit of avapritinib, results from the double-blind, randomised comparison with best supportive care from the PIONEER study are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects.

With regard to overall survival, there were no deaths in either study arm. From the available data, there is therefore no relevant difference.

In the morbidity endpoint category, results are available on patient-reported symptomatology (ISM-SAF, PGIS) and health status (EQ-5D VAS).

The results of the ISM-SAF responder analysis show a relevant advantage of treatment with avapritinib with regard to skin symptoms. However, there was no difference with regard to other relevant symptoms in the gastrointestinal and neurocognitive areas. The analysis of the individual lead domain showed a clinically relevant advantage of avapritinib.

An advantage of treatment with avapritinib is also shown in the PGIS and EQ-5D VAS endpoints.

Overall, the advantages in the endpoint category of morbidity are assessed as previously unattained moderate improvement in the therapy-relevant benefit and not just a slight one.

Results of the SF-12 and the MC-QoL are available for the endpoint category of health-related quality of life. The physical component summary of the SF-12 endpoint shows an advantage of avapritinib. For the present differences in MC-QoL, it cannot be concluded with sufficient certainty that the observed effect is clinically relevant.

With regard to side effects, the results show no relevant differences for the assessment.

In the overall assessment, treatment with avapritinib showed a relevant improvement in terms of skin symptoms compared to best supportive care, but not for other significant symptoms. Therefore, these results are assessed overall as a relevant improvement in symptomatology, which justify a minor but not a considerable additional benefit in the overall assessment. This assessment of the extent of the additional benefit is also supported by the results on health-related quality of life. The G-BA therefore categorised the extent of the additional benefit of avapritinib for the treatment of adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment as minor.

Significance of the evidence

This assessment is based on the randomised, controlled second part of the PIONEER study.

The risk of bias at study level and for the primary endpoint of ISM-SAF is assessed as low.

Overall, the significance is classified in the "indication" category.

2.1.3 Summary of the assessment

The present assessment is a benefit assessment of a new therapeutic indication for the active ingredient avapritinib. Ayvakyt has been conditionally approved as an orphan drug for the treatment of adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment.

The benefit assessment of avapritinib is based on the completed, double-blind, randomised second part of the PIONEER study, in which avapritinib was compared with placebo, in each case in combination with BSC, over 24 weeks.

With regard to overall survival, no deaths occurred in either study arm. From the available data, there is therefore no relevant difference.

In the morbidity endpoint category, results are available on patient-reported symptomatology (ISM-SAF, PGIS) and health status (EQ-5D VAS).

The results of the ISM-SAF responder analysis show a relevant advantage of treatment with avapritinib with regard to skin symptoms. However, there was no difference with regard to other relevant symptoms in the gastrointestinal and neurocognitive areas. The analysis of the individual lead domain showed a clinically relevant advantage of avapritinib.

An advantage of treatment with avapritinib is also shown in the PGIS and EQ-5D VAS endpoints.

Results of the SF-12 and the MC-QoL are available for the endpoint category of health-related quality of life. The physical component summary of the SF-12 endpoint shows an advantage of avapritinib. For the present differences in MC-QoL, it cannot be concluded with sufficient certainty that the observed effect is clinically relevant.

With regard to side effects, the results show no relevant differences for the assessment.

In the overall assessment, the G-BA classifies the extent of the additional benefit of avapritinib as minor, based on the benefits in the endpoint categories of morbidity and health-related quality of life.

The significance of the evidence is categorised in the "indication" category.

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

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

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The patient numbers are subject to uncertainties.

The pharmaceutical company determines the number of patients using an 8-step procedure.

The uncertainties in the patient numbers result from the diagnosis code used, which does not exclusively include indolent systemic mastocytosis, and from the fact that the pharmaceutical company does not use the range but the mean value as the basis for extrapolation to the total SHI population, thus not taking the given uncertainty into account.

A further uncertainty results from the percentage values used to determine the percentage of patients in the indication of indolent systemic mastocytosis inadequately controlled on symptomatic therapy. The pharmaceutical company states a range of 25% to 35% for this percentage of patients. This range is based on expert opinions without any further information on their assessment.

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 Ayvakyt (active ingredient: avapritinib) at the following publicly accessible link (last access: 4 April 2024):

https://www.ema.europa.eu/documents/product-information/ayvakyt-epar-product-information_de.pdf

Treatment with avapritinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of indolent systemic mastocytosis.

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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 June 2024).

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

Treatment period:

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.

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

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Avapritinib	25 mg	25 mg	1 x 25 mg	365	365 x 25 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.

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					
Avapritinib 25 mg	30 FCT	€ 16,868.70	€ 2.00	€ 962.78	€ 15,903.92
Abbreviations: FCT = film-coated tablets					

LAUER-TAXE® last revised: 1 June 2024

Costs for additionally required SHI services:

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

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

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

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

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

Basic principles of the assessed medicinal product

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

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

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of

designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

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

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

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

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

Concomitant active ingredient

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

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

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

Adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for avapritinib (AYVAKYT); AYVAKYT® 25 mg/ -50 mg/ -100 mg/ -200 mg/-300 mg film-coated tablets; last revised: April 2024

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 20 December 2023 the pharmaceutical company submitted a dossier for the benefit assessment of avapritinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

The benefit assessment of the G-BA was published on 2 April 2024 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 23 April 2024.

The oral hearing was held on 6 May 2024.

An amendment to the benefit assessment with a supplementary assessment was submitted on 28 May 2024.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI

umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 11 June 2024, and the proposed resolution was approved.

At its session on 20 June 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 June 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	30 April 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 May 2024	Conduct of the oral hearing
Working group Section 35a	15.05.2024; 05.06.2024	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	11 June 2024	Concluding discussion of the draft resolution
Plenum	20 June 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 June 2024

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

Prof. Hecken