Gemeinsamer Bundesausschuss

Justification

for the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Avapritinib (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit (indolent systemic mastocytosis (ISM))

dated 7 May 2026

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

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

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

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

2. Key points of the resolution

The active ingredient 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. Ayvakyt for the treatment of indolent systemic mastocytosis 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.

At their session on 20 June 2024, the G-BA adopted a resolution on the benefit assessment of avapritinib for the therapeutic indication "Treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment" in accordance with Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must

submit evidence in accordance with Chapter 5 Section 5, paragraphs 1 to 6 Rules of Procedure (VerfO) within three months of being requested to do so by the Federal Joint Committee, and in this evidence, must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 16 July 2025, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 November 2025, due to exceeding EUR 30 million turnover limit within the period from April 2024 to March 2025. Pursuant to Section 4, paragraph 3, No. 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, No. 4 Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 30 October 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 February 2026 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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 07.05.2026):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for avapritinib:

- Best supportive care

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

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

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

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

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

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

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

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

On 1. Apart from avapritinib, no other medicinal products are approved for the present therapeutic indication.

On 2. Non-medicinal treatments are not indicated.

On 3. A resolution of the G-BA on Annex VI to Section K and Annex I to Section F of the Pharmaceuticals Directive is available.

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (so-called off-label use); part A:

- IV. Disodium cromoglycate (DNCG)-containing medicinal products (oral) for systemic mastocytosis

Annex I to Section F of the Pharmaceuticals Directive Statutory exclusions from prescription in medicines supply and approved exceptions; approved exceptions to the statutory exclusion from prescription pursuant to Section 34, paragraph 1, sentence 2 SGB V (OTC overview)

- 15. Disodium cromoglycate (DNCG)-containing medicinal products (oral) only for the symptomatic treatment of systemic mastocytosis

On 4. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy"). In this regard, an opinion passed by the German Society for Haematology and Medical Oncology (DGHO) is available.

Overall, the evidence on treatment options in this therapeutic indication is extremely limited. No methodologically sound reviews or guidelines could be identified during the systematic search. Consequently, the National Comprehensive Cancer Network (NCCN) guideline was additionally used.

The NCCN guideline and clinical experts initially recommend symptom-based treatment in the form of best supportive care (BSC) for the management of symptomatic ISM. For the present therapeutic indication, the following active ingredients are considered suitable for BSC: H1 and H2 receptor antagonists, leukotriene antagonists, cromoglicic acid (see Annexes I and VI to the Pharmaceuticals Directive), glucocorticoids, proton pump inhibitors, omalizumab, epinephrine, bisphosphonates and other active ingredients. The active ingredients mentioned above are not approved for the treatment of ISM, but only for the treatment of mediator-related symptoms or, in this context, are eligible for prescription (cromoglicic acid).

In the case of inadequate response or persistent symptomatology, the NCCN guideline and clinical experts recommend the active ingredient avapritinib. When determining the appropriate comparator therapy, the actual medical treatment situation as it would be without avapritinib must however be taken into account.

In this regard, in addition to symptom-based therapy, the NCCN guideline recommends cladribine, peginterferon alfa-2a +/- prednisone and midostaurin apart from avapritinib. Cladribine, peginterferon alfa-2a +/- prednisone and midostaurin are not approved in the present therapeutic indication.

In line with the statements made by the clinical experts in this benefit assessment procedure, therapy with cladribine, peginterferon alfa-2a +/- prednisone or midostaurin is only considered in isolated cases for patients in the present therapeutic indication.

In the overall assessment, BSC is therefore determined to be the appropriate comparator therapy. Best supportive care (BSC) is defined as the therapy that provides the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

Change in the appropriate comparator therapy

In the originally determined appropriate comparator therapy, an individualised therapy, which, in addition to best supportive care, includes cladribine, peginterferon alfa-2a +/- prednisone and midostaurin as treatment options, was considered a suitable comparator therapy. However, this does not reflect the typical medical treatment situation according to the statements made by clinical experts in the present benefit assessment procedure. The clinical experts note that cladribine, peginterferon alfa-2a +/- prednisone and midostaurin are only considered in isolated cases in this therapeutic indication and should therefore not be regarded as therapy standard. Taking into account the additional aspects above regarding these treatment options, the G-BA consider it appropriate to change the appropriate comparator therapy for the present resolution accordingly and to determine best supportive care alone as the appropriate comparator therapy.

As a result of the change in the appropriate comparator therapy, the present assessment now has a different starting point for the assessment of the implementation of the appropriate comparator therapy in the PIONEER study, on which the benefit assessment is based.

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

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

2.1.3 Extent and probability of the additional benefit

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

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

Hint for 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.

The PIONEER study is an ongoing phase II study divided into three parts. The first part of the study was a dose-ranging phase. In the second part, avapritinib was compared with placebo, each in combination with best supportive care, in a double-blind, randomised study phase over a period of 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.

In the completed second part of the study, a total of 212 patients aged between 18 and 79 years with a confirmed diagnosis of indolent systemic mastocytosis were enrolled in the study; these were patients, in whom, in the opinion of the principal investigator, adequate symptom control for at least 1 symptom could not be achieved with at least 2 symptomatic therapies, and who, despite symptomatic therapy, had a total symptom score (TSS) ≥ 28 on the *Indolent*

Systemic Mastocytosis Symptom Assessment Form (ISM-SAF). The patients enrolled were randomised in a 2:1 ratio to the two study arms (avapritinib: N = 141; placebo: N = 71).

The pharmaceutical company presented the results for the final data cut-off from 23.06.2022.

On the implementation of Best Supportive Care (BSC)

The BSC planned in both arms included, amongst other things, H1 and H2 antihistamines, proton pump inhibitors, osteoclast inhibitors, leukotriene inhibitors, glucocorticoids (≤ 20 mg prednisone or equivalent), mast cell stabilisers (e.g. cromoglicic acid) and anti-immunoglobulin E antibodies (omalizumab).

The active ingredients covered by BSC in the PIONEER study are considered suitable for the implementation of BSC in a clinical study in the present therapeutic indication.

By amendment 7 of 01.11.2021 to the study protocol, it was stipulated that glucocorticoid therapy should not be initiated in patients who were not receiving glucocorticoids at the start of the study. The dose should not be increased in patients who were already receiving glucocorticoid therapy at the start of the study. As part of the written statement procedure, the pharmaceutical company stated that only a negligible number of patients were enrolled following the entry into force of Amendment 7; however, exact figures are not available.

The clinical experts emphasised at the oral hearing that long-term use of glucocorticoid therapy should be avoided - despite being an effective treatment option for this therapeutic indication - due to the side effects associated with prolonged treatment, such as osteoporosis.

However, the categorical limitation of treatment with glucocorticoids by Amendment 7 is viewed critically by the G-BA in the overall assessment and is regarded as uncertainty regarding the implementation of the BSC .

Despite this limitation, sufficient approximation of the appropriate comparator therapy is assumed overall, and the results of the PIONEER study are used for the benefit assessment. However, uncertainty regarding the implementation of the BSC in the PIONEER study remains.

Extent and probability of the additional benefit

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.

For the benefit assessment, the responder analyses presented by the pharmaceutical company regarding the percentage of subjects showing an improvement by at least 15% of the scale range (TSS ≥ 16.5 points, domains ≥ 4.5 points) at week 24 were used.

For the ISM-SAF endpoint, a statistically significant difference in favour of avapritinib was observed in the skin domain. No statistically significant differences were observed between the study arms in the TSS as well as in the domains of gastrointestinal and neurocognitive symptomatology.

The pharmaceutical company also submitted analyses of the mean change in the individual cardinal symptom and the cardinal domain.

Patients with ISM experience a wide range of symptoms. Given the heterogeneous clinical picture of ISM and the individual variation in the manifestation of conditions, the analyses of the cardinal symptom and the cardinal domain are used for the benefit assessment.

Both the cardinal symptom and the cardinal domain showed a significant improvement in the mean difference in the avapritinib arm. The 95% confidence interval for the standardised mean difference (Hedges' g) of the cardinal domain lies outside the irrelevance threshold (-0.2 to 0.2), meaning that the effect is classified as clinically relevant. This is not the case for the cardinal symptom, so it cannot be concluded with sufficient certainty that the observed effect is clinically relevant for the cardinal symptom.

Patient Global Impression of Symptom Severity (PGIS)

The PGIS is used in the PIONEER study in addition to the ISM-SAF to survey symptomatology. The PGIS includes a question asking patients to rate the severity of their symptoms on a 5-point scale (from 0 = absent to 4 = very severe).

For the benefit assessment, the responder analyses presented by the pharmaceutical company regarding the percentage of subjects showing an improvement by at least 15% of the scale range (≥ 1 point) at week 24 were used.

There was a statistically significant difference in favour of avapritinib for the PGIS.

Patient Global Impression of Change (PGIC)

The PGIC is used to assess changes in activity limitations, symptoms, emotions and overall quality of life. 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. The possible responses included various options for improvements, as well as an option for no change, including deterioration. It is therefore not possible to distinguish between "no change" and "deterioration". Higher scores in this item indicate an improvement.

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

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

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

The health status was assessed in the PIONEER study using the visual analogue scale (VAS) of the EQ-5D.

For the benefit assessment, the responder analyses presented by the pharmaceutical company regarding the percentage of subjects showing an improvement by at least 15% of the scale range (≥ 15 points) at week 24 were used.

There was a statistically significant difference in favour of avapritinib for the EQ-5D VAS.

Conclusion on the morbidity endpoint category

For the ISM-SAF endpoint, a statistically significant difference in favour of avapritinib was observed in the skin domain. No statistically significant differences were observed between the study arms in the TSS as well as in the domains of gastrointestinal and neurocognitive symptomatology.

Change in individual symptomatology was assessed using the ISM-SAF by analysis of the individual cardinal symptom and cardinal domain. The analysis of the individual cardinal domains showed a clinically relevant advantage of avapritinib.

Symptomatology was also assessed using the PGIS, and health status using the EQ-5D VAS and PGIC. For the PGIS and EQ-5D VAS endpoints, there was a statistically significant difference in favour of avapritinib in each case. There was no statistically significant difference between the study arms for the PGIC.

Quality of life

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

Mastocytosis Quality of Life Questionnaire (MC-QoL)

The MC-QoL was used to assess disease-specific quality of life. The questionnaire comprises 27 items covering the domains of symptoms, emotions, social life/ functioning 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, followed by linear transformation on a scale from 0 to 100. A higher score indicates a greater impairment of quality of life.

For the benefit assessment, the responder analyses presented by the pharmaceutical company regarding the percentage of subjects showing an improvement by at least 15% of the scale range (≥ 15 points) at week 24 were used.

For the MC-QoL endpoint, statistically significant differences in favour of avapritinib were observed in the total score and in the domains of symptoms, emotions, and social life/ functioning. In the skin domain, there was no statistically significant difference between the study arms.

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.

For the benefit assessment, the responder analyses presented by the pharmaceutical company regarding the percentage of subjects showing an improvement by ≥ 9.1 points on the PCS or an improvement by ≥ 8.5 points on the MCS at week 24 were used. The threshold for clinically relevant improvement was determined using the 2009 normative sample. The approach is rated as appropriate.

There was a statistically significant difference in favour of avapritinib for the PCS of SF-12. There was no statistically significant difference between the study arms for the MCS of SF-12.

Conclusion on the health-related quality of life endpoint category

Results of the MC-QoL and the SF-12 are available for the endpoint category of health-related quality of life. For the MC-QoL endpoint, statistically significant differences in favour of avapritinib were observed in the total score and in the domains of symptoms, emotions, and social life/ functioning. In the skin domain, there was no statistically significant difference between the study arms.

There was a statistically significant difference in favour of avapritinib for the PCS of SF-12. There was no statistically significant difference between the study arms for the MCS of SF-12.

Side effects

Total adverse events (AEs) (presented additionally)

In the PIONEER study, adverse events occurred in 90.8% of patients in the intervention arm and 93.0% of patients in the control arm. The results were only presented additionally.

Serious AEs (SAEs) Severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs

For the endpoints of SAEs, severe AEs and therapy discontinuation due to AEs, there was no statistically significant difference between the study arms in each case.

Specific AEs

No specific AEs were identified.

Overall assessment

The pharmaceutical company presented the results from the PIONEER study for the assessment of the additional benefit of avapritinib for the treatment of adults with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment. In the completed, double-blind, randomised second part of the study, avapritinib was compared with placebo, each in combination with BSC, over 24 weeks. Results on the endpoint categories of mortality, morbidity, quality of life and side effects are available.

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

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

For the ISM-SAF endpoint, a statistically significant difference in favour of avapritinib was observed in the skin domain. No statistically significant differences were observed between the study arms in the TSS as well as in the domains of gastrointestinal and neurocognitive symptomatology.

Change in individual symptomatology was assessed using the ISM-SAF by analysis of the individual cardinal symptom and cardinal domain. The analysis of the individual cardinal domains showed a clinically relevant advantage of avapritinib.

Symptomatology was also assessed using the PGIS, and health status using the EQ-5D VAS and PGIC.Statistically significant differences in favour of avapritinib were observed in the PGIS and EQ-5D VAS. There was no statistically significant difference between the study arms for the PGIC.

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 minor one.

In the endpoint category of quality of life, results of the MC-QoL and SF-12 are available.

For the MC-QoL endpoint, statistically significant differences in favour of avapritinib were observed in the total score and in the domains of symptoms, emotions, and social life/ functioning. In the skin domain, there was no statistically significant difference between the study arms.

There was a statistically significant difference in favour of avapritinib for the PCS of SF-12. There was no statistically significant difference between the study arms for the MCS of SF-12.

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

In the overall assessment of symptomatology, treatment with avapritinib showed a relevant improvement in terms of skin symptomatology compared to best supportive care, but not for other significant symptoms. Relevant improvements are also evident in the endpoint category of quality of life. These results are assessed overall as a relevant improvement, which justify a minor but not a considerable additional benefit in the overall assessment.

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.

Reliability of data (probability of additional benefit)

This assessment is based on the double-blind, randomised second part of the PIONEER study.

Due to the limitations of glucocorticoid therapy, the implementation of the appropriate comparator therapy and, consequently, the transferability of the study results to the German healthcare context is subject to uncertainty.

Overall, a hint is derived for the reliability of data of the additional benefit identified.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the medicinal product Ayvakyt with the active ingredient avapritinib due to exceeding the EUR 30 million turnover limit. Ayvakyt was approved as an orphan drug. The therapeutic indication assessed here is as follows:

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

The G-BA determined Best Supportive Care (BSC) to be the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company submitted the results of the PIONEER study. In the completed, double-blind, randomised second part of the study, avapritinib was compared with placebo, each in combination with BSC, over 24 weeks.

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

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

In the skin domain of the ISM-SAF, the individual cardinal domain using the ISM-SAF, in the PGIS and EQ-5D VAS, statistically significant advantages of avapritinib were observed.

In the endpoint category of quality of life, results of the MC-QoL and SF-12 are available.

In the total score as well as in the domains of symptoms, emotions and social life/ functioning of the MC-QoL and the PCS of SF-12, statistically significant advantages of avapritinib were observed.

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

In the overall assessment of symptomatology, treatment with avapritinib showed a relevant improvement in terms of skin symptomatology compared to BSC, but not for other significant symptoms. Relevant improvements are also evident in the endpoint category of quality of life. These results are assessed overall as a relevant improvement, which justify a minor but not a considerable additional benefit in the overall assessment.

The G-BA therefore classify the extent of the additional benefit of avapritinib as minor.

The reliability of data is classified in the "hint" category. This is due to uncertainty regarding the implementation of BSC in the PIONEER study, which stems from a limitation on glucocorticoid therapy during the course of the study.

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 uncertainty.

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

The uncertainty in the patient numbers results 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.

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. The range given is based on expert opinions without sufficient information on its 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: 29 January 2026):

https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.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 (EMA) will assess new information on this medicinal product at least annually and update the product information where necessary.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 February 2026).

The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

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.

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

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

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:				
Avapritinib	Continuously, 1 x daily	365.0	1	365.0
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

Consumption:

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

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	365.0	365 x 25 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				

Costs:

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

Costs of the medicinal products:

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

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed:					
Avapritinib 25 mg	30 FCT	€ 15,149.74	€ 1.77	€ 864.61	€ 14,283.36
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Abbreviations: FCT = film-coated tablets					

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Costs for additionally required SHI services:

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

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

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

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

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

Basic principles of the assessed medicinal product

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

sections of the currently valid product information for the assessed medicinal product.

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

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

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

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

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

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

Concomitant active ingredient

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

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the

date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

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

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

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

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

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

Designation

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

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

Exception to the designation

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

preceding findings were based.

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

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between statutory health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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

Justification for the findings on designation in the present resolution:

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

No medicinal product with new active ingredients for use in combination therapy in compliance with 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

At their session on 27 May 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 October 2025, 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 6 VerfO.

By letter dated 30 October 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient avapritinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 January 2026, and the written statement procedure was initiated with publication on the website of the G-BA on 2 February 2026. The deadline for submitting written statements was 23 February 2026.

The oral hearing was held on 9 March 2026.

By letter dated 10 March 2026, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 10 April 2026.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the Subcommittee on 28 April 2026, and the draft resolution was approved.

At their session on 7 May 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	27 May 2025	Determination of the appropriate comparator therapy
Working group Section 35a	4 March 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	9 March 2026	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 March 2026 22 April 2026	Consultation on the dossier assessment by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	28 April 2026	Concluding discussion of the draft resolution
Plenum	7 May 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 7 May 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken