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, systemic mastocytosis, after at least 1 prior therapy)

of 15 September 2022

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 € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

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

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 legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and 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 24 March 2022, Ayvakyt 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, 12.12.2008, p. 7).

Ayvakyt for the treatment of adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy, is authorised 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 and probability of the additional benefit are assessed on the basis of the approval studies by the G-BA.

On 31 March 2022, i.e. at the latest within four weeks after the pharmaceutical company has been notified of the authorisation for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient avapritinib with the new therapeutic indication (advanced systemic mastocytosis (AdvSM)).

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 1 July 2022 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G22-10) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering 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.

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

2.1 Additional benefit of the medicinal product

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

AYVAKYT is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy.

Therapeutic indication of the resolution (resolution of 15 September 2022):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy

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

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

Justification:

To assess the additional benefit of avapritinib, the pharmaceutical company presented data from the single-arm pivotal PATHFINDER and EXPLORER studies as well as pooled analyses of both studies in the dossier. Results were also presented from two indirect comparisons of avapritinib cohorts, based on data from the PATHFINDER and EXPLORER studies, with retrospective observational data (BLU-285-2405) and with aggregated study data on midostaurin (Pilkington et al., 2022).

In the dossier for the PATHFINDER and EXPLORER studies, the pharmaceutical company evaluates in each case the pivotal patient population with advanced systemic mastocytosis (AdvSM) and at least one prior therapy, who also received the avapritinib pivotal dose of 200 mg. The respective assessment-relevant sub-population of the EXPLORER and PATHFINDER studies submitted by the pharmaceutical company is used for the benefit assessment.

PATHFINDER study

The ongoing pivotal PATHFINDER study is an uncontrolled phase II study. The PATHFINDER study includes two cohorts. Cohort 1 includes patients who have evaluable disease (an evaluable C finding or mast cell leukaemia (MCL)) as assessed by the Study Steering Committee using the mIWG-MRI-ECNM criteria. Cohort 2 includes those patients with centrally confirmed aggressive systemic mastocytosis (ASM) or with systemic mastocytosis with associated haematological neoplasm (SM-AHN) who, according to the Study Steering Committee, have no evaluable C findings.

The clear majority of patients had 1-2 prior therapies and had been pretreated with midostaurin (tyrosine kinase inhibitor (TKI)), the only other medicinal product currently approved in the therapeutic indication (≥ 84%). Accordingly, approx. 96% of the subjects were pretreated with a TKI therapy.

About 21% were diagnosed with aggressive systemic mastocytosis (ASM), about 61% were diagnosed with systemic mastocytosis with associated haematological neoplasm (SM-AHN) and about 18% were diagnosed with mast cell leukaemia (MCL). According to the EMA, these classifications of AdvSM have very variable survival prognoses. With regard to mutations, almost all patients (97%) showed a KIT exon 17 mutation. Most subjects had an ECOG-PS (Eastern Cooperative Oncology Group – Performance Status) of 0-2.

Patients in the study were treated in continuous cycles (28 days) until there was a reason for therapy discontinuation and a subsequent visit at the end of treatment. Follow-up with regard to safety endpoints was by telephone up to 30 days after therapy discontinuation, every 24 weeks until disease progression or initiation of other cytostatic therapy for response investigation, and every 12 weeks for overall survival. Of the patients with ≥ 1 prior antineoplastic therapy (safety population, n = 69), 67 patients received a pivotal avapritinib dose.

The study is being conducted in 10 study sites in North America and 8 in Europe. Enrolment took place between 2018 and 2021. The primary endpoint is the adjusted overall response rate (adj. ORR = CR/CRh + PR + CI). Secondary endpoints include overall survival, endpoints on morbidity and health-related quality of life, and side effects.

The second and currently most up-to-date data cut-off of the study from 20 April 2021 (EMA requirement) is used for the benefit assessment. None of the interim analyses was pre-specified before the start of the study. Just under 75% of the study population continue to participate in the study at the data cut-off and about 70% still undergo treatment.

<u>EXPLORER study</u>

The ongoing supportive EXPLORER study is an uncontrolled phase I study with a phase II expansion. This comprises two parts (Part I and Part II), with Part II again divided into two cohorts. Part I is a dose escalation phase and Part II is an extension phase. Cohort 1 includes patients without evaluable C findings at baseline, while participants in cohort 2 have at least one measurable C finding.

The clear majority of patients had 1-2 prior therapies and had been pretreated with midostaurin (tyrosine kinase inhibitor (TKI)), the only other medicinal product currently approved in the therapeutic indication (≥ 84%). All subjects in the pivotal sub-population were pretreated with TKI therapy.

About 8% were diagnosed with aggressive systemic mastocytosis (ASM), about 58% with systemic mastocytosis with associated haematological neoplasm (SM-AHN) and about 33% were diagnosed with mast cell leukaemia (MCL). Descriptively, there are significantly fewer C findings than in the PATHFINDER study. With regard to mutations, approx. 83% of the patients showed a KIT exon 17 mutation. Most subjects had an ECOG-PS (Eastern Cooperative Oncology Group – Performance Status) of 0-2. With regard to ECOG-PS, the distribution of patients was similar to that in the PATHFINDER study.

During the course of the study, there will be continuous treatment with avapritinib after enrolment in the study and a visit at the end of treatment 14 days after the last study medication. A safety follow-up was conducted by telephone 30 days after administration of

the last study medication, and from protocol endpoint 6, a telephone follow-up regarding survival was conducted approximately every 3 months. Of the patients with ≥ 1 prior antineoplastic therapy (safety population, n = 41), 12 patients received a pivotal avapritinib dose.

The study is being conducted in 10 study sites across North America and Great Britain. Enrolment took place between 2016 and 2021. Primary endpoints of the study are the incidence of adverse events (AEs) as well as dose-limiting toxicity.

The second and currently most up-to-date data cut-off of the study from 20 April 2021 (EMA requirement) is used for the benefit assessment. None of the interim analyses was pre-specified before the start of the study. About two-thirds of the study population (about 67%) continue study participation at the data cut-off and half of the study participants still undergo treatment.

On the indirect comparisons presented

BLU-285-2405 study (PATHFINDER and EXPLORER studies (pooled) versus BAT cohort)

The BLU-285-2405 study is a propensity score (PS)-adjusted indirect comparison without a bridge comparator for the therapeutic indication of advanced systemic mastocytosis. The report compares patients treated with avapritinib from the PATHFINDER and EXPLORER studies (pooled) with patients who, according to the pharmaceutical company, were treated with the best available treatment (BAT). A clear definition of the BAT was missing. In addition, it was not comprehensible whether the therapies applied in each case were actually the best available therapies. For the benefit assessment, on the side of the intervention group, the sub-population of patients from the pooled PATHFINDER and EXPLORER studies who received 200 mg avapritinib and at least one prior therapy (N = 79) and, on the side of the control group, the sub-population of patients from the BAT cohort who received at least one prior therapy (N = 73) are relevant. According to the protocol information, interventions in the BAT cohort could include midostaurin, cytoreductive therapies (cladribine, interferon-alfa, azacitidine, decitabine), other tyrosine kinase inhibitors (imatinib, nilotinib, dasatinib, ripretinib) and hydroxyurea. The information from the BAT cohort was extracted from patient records between 2009 and 2021 and came from 6 study sites (USA, UK, Spain, Austria and Germany). The data cut-off took place on 4 October 2021. For the BLU-285-2405 study, the pharmaceutical company submits complete documentation in the dossier and presents the results on the endpoints of overall survival, treatment duration and change in serum tryptase levels in Module 4.

The inclusion and exclusion criteria used for the BAT cohort differed in part from those used for the avapritinib cohort. Balancing the inclusion and exclusion criteria was only addressed for a few factors by adjusting the analysis population and was thus not always achieved. This concerns, among others, the criteria of confirmation type of AdvSM diagnosis, measurable C findings, requirements for laboratory parameters, ECOG-PS / Karnofsky score, exclusion of requirement regarding other diagnoses and therapies.

There is no information in the dossier on a systematic literature search and assessment to identify confounders for the question addressed in the benefit assessment. Consequently, essential information on the selection of the confounders and the confounder characteristics applied in the indirect comparison is missing. Based on the aspects discussed in the oral hearing on the present benefit assessment procedure, it can be assumed that very little or no information is available on a large part of the covariates for the rare disease in question.

However, this does not mean that a systematic literature search and assessment for the possible identification of relevant confounders can be dispensed with from the outset.

Key covariates for the propensity score-adjusted indirect comparison were defined as covariates that should be included in the propensity score model independently of quantitative criteria. In this regard, 13 obligate key covariates were listed for consideration in the propensity score adjustment. As a result, differences in at least 7 of the 13 key covariates considered could not be compensated for by propensity score adjustment according to the pre-specified balance threshold of a standardised difference of > 10% in the analysis of overall survival (OS).

In addition to the key covariates, further baseline characteristics were defined as covariates in the statistical analysis plan. With regard to these covariates, it was pre-specified that a balance test between the groups under investigation should be carried out first. In the case of a corresponding difference of > 10%, it was also planned to include the corresponding covariates in the propensity score model. As a result, there is no data available on the pre-specified balance test of these further covariates in the dossier and it is assumed that these covariates were not included in the propensity score model for adjustment.

During the oral hearing on the present benefit assessment procedure, the prognostic significance of some covariates that were not included in the propensity score model for adjustment was discussed. These included: the BMI (body mass index), number of co-mutations, mast cell infiltration in the bone marrow or presence of mast cell aggregates, various laboratory measurements, comorbidities, symptoms associated with mast cell activation, stem cell transplant, point of treatment of the subjects. As a result, the prognostic significance of these covariates cannot be conclusively assessed, even taking into account the assessments presented by the scientific-medical societies.

In addition, the handling of missing values, especially for some key covariates in the analysis, is sometimes unclear or inadequate, which means that systematic bias in the results of the analysis cannot be ruled out.

Overall, a lack of structural equality of the patient populations with regard to clinically relevant confounders for the indirect comparison presented cannot therefore be excluded with sufficient certainty.

In addition to the points of criticism already described, there were numerous other points of criticism of the submitted indirect comparison in the benefit assessment. These were largely addressed by the pharmaceutical company in the written statement procedure, but essentially not rejected, among other things also by referring to a population in the written statement procedure that differed from the corresponding pivotal sub-population in the benefit assessment.

Overall, the results of the indirect comparison presented are therefore fraught with considerable uncertainties.

In the BLU-285-2405 study, evaluations are only available for one patient-relevant efficacy endpoint of overall survival.

Taking into account the considerable uncertainties of the indirect comparison presented, the results in the endpoint of overall survival do not indicate an effect of a magnitude for which it

can be assumed with sufficient certainty that the observed differences are not due to systematic bias alone.

As a result, the submitted indirect comparison is not used for the present benefit assessment.

Pilkington et al. (2022) (external control study, indirect comparison)

With the dossier, the pharmaceutical company has submitted a publication on an indirect comparison of avapritinib with midostaurin in patients with advanced systemic mastocytosis (Pilkington et al., 2022).

A systematic literature review was conducted as the basis for the indirect comparison. The single-arm PATHFINDER and EXPLORER studies regarding treatment with avapritinib and 2 further single-arm D2201 and A2213 studies regarding treatment with midostaurin were identified. These were pooled intervention-specifically in each case and indirectly compared with each other with regard to the endpoints of OS, ORR and CR on the basis of the aggregated data. The comparative analyses were carried out using naïve indirect comparisons and (unanchored) matching-adjusted indirect comparisons (MAIC).

The indirect comparison by Pilkington et al. (2022) submitted by the pharmaceutical company is not used for the benefit assessment of avapritinib, mainly due to the limited study documents submitted, which do not allow an adequate methodological assessment in the context of the benefit assessment, and due to the conduct of the indirect comparisons on an aggregated (pooled) study level without using complete patient-individual data. MAIC analyses with aggregated data without a bridge comparator are generally not an adequate way to adjust for confounders.

On the results of the PATHFINDER and EXPLORER studies by endpoint:

Mortality

The overall survival was defined in the PATHFINDER and EXPLORER studies as the time from first administration of the study medication to death from any cause. For overall survival, no pooled presentation of the results is given due to the large differences in the follow-up durations of the studies and the initially divergent follow-up after disease progression or after the start of antineoplastic therapy.

At the data cut-off from 20.04.2021, it can be seen across both studies that about 73% of the patients enrolled so far are still participating in the study and 67% are still taking their study medication. The results for the endpoint of overall survival from both studies are uncertain, especially due to the low event rates in the study arms so far: The median survival time had not yet been reached in either study by the time of the data cut-off.

Due to the single-arm study design, a comparative assessment of the results on overall survival is not possible. The effect of avapritinib on mortality cannot be conclusively assessed on the basis of the data presented.

Morbidity

Complete remission (CR)

The overall response rate (ORR) in the PATHFINDER and EXPLORER studies is defined as the percentage of patients with a confirmed best response as CR, complete remission with partial recovery of peripheral blood count (CRh), partial response (PR) or clinical improvement (CI), each according to mIWG criteria.

The primary endpoint in the PATHFINDER study is the adjusted ORR, which was assessed by a central Study Committee.

The change of the IWG criteria to the mIWG criteria within the EXPLORER study, which was accompanied by the inclusion of CRh as a component of the ORR, is being viewed critically.

The mIWG criteria were used prospectively in the PATHFINDER study.

Based on the rationale for including CRh in the definition of ORR as outlined in the EXPLORER study documents, the inclusion of CRh in the mIWG criteria is assumed to be outcome-driven. Therefore, complete remission (CR) is presented additionally as an alternative to ORR as part of the primary endpoint ORR.

Operationalisation of the response criteria is based almost exclusively on laboratory parametric and histological findings. If the response is assessed almost exclusively on the basis of laboratory parametric and histological findings, the assessment of morbidity is not primarily based on disease symptoms, but on asymptomatic findings that are not directly patient-relevant.

As a result, the endpoint overall response rate (ORR) is not used for the benefit assessment. The subcomponent complete remission (CR) is presented additionally.

Patient's Global Impression of Symptom Severity (PGIS)

The PGIS is a patient-reported tool to assess the severity of a disease. It consists of one item ("right now, the symptoms of my systemic mastocytosis are") and the assessment is done on a five-point scale.

When interpreting the results on the PGIS, it should be taken into account that the endpoint is collected for different lengths of time in the two studies (up to cycle 17 in the PATHFINDER study and up to cycle 12 in the EXPLORER study) and that the treatment duration differs significantly in the two studies. Nevertheless, both studies show similarly decreasing return rates, which makes a pooled evaluation of the results up to cycle 3 possible. Only descriptive results for continuous change compared to baseline are presented in each case.

The mean value of the PGIS (range: 0-4) is 2.5 at baseline on a pooled level and 1.5 in cycle 3.

Due to the single-arm study design, a comparative assessment of the data on PGIS is not possible.

Symptomatology

Disease symptomatology was assessed in the PATHFINDER and EXPLORER studies using the symptom scales of the EORTC QLQ-C30 questionnaire. In the dossier, the pharmaceutical

company presents evaluations of the changes in the EORTC symptom scales compared to baseline.

When interpreting the results, it should be taken into account, as with the PGIS, that the assessment was conducted for different lengths of time in the two studies (PATHFINDER up to cycle 17 and EXPLORER up to cycle 12) and that the treatment duration in the two studies differed significantly. Nevertheless, both studies show sufficiently similar decreasing return rates to allow a pooled presentation of the results up to cycle 3.

Due to the single-arm study design, a comparative assessment of the data on EORTC QLQ-C30 is not possible.

Quality of life

Health-related quality of life was assessed in the PATHFINDER and EXPLORER studies using the functional scales and the global scale of general health status of the EORTC-QLQ-C30 questionnaire.

The survey time points differ between the PATHFINDER and EXPLORER studies. In the PATHFINDER study, the survey is conducted more closely at each visit from cycle 1 day 1 to cycle 17 or until the end of treatment. In the EXPLORER study, the EORTC QLQ-C30 is only collected in Part II and on the first day of each of cycles 1 to 12.

The pharmaceutical company presents results in the dossier on the changes in the functional scales and the general health status scale compared to baseline. The results are presented for each study as long as a return rate of ≥ 70% is achieved (exception: cycle 3 of the EXPLORER study).

Due to the single-arm study design, a comparative assessment of the data on EORTC-QLQ-C30 is not possible.

Side effects

Follow-up upon occurrence of safety events in the PATHFINDER and EXPLORER studies will be continuous during therapy with avapritinib up to 30 days after administration of the last study medication.

The median duration of treatment at the 20.04.2021 data cut-off is just over 9 months in the PATHFINDER study, just under 21 months in the Explorer study and just under 10 months in the pooled analysis. The almost twice as long median treatment duration of the EXPLORER study compared to the PATHFINDER study must be taken into account when interpreting the results. In addition, when interpreting the results on the AEs, it must be taken into account that the AEs surveyed may include symptoms of the underlying disease.

Adverse events occurred in all patients in both studies. AEs of CTCAE grade ≥ 3 were documented in 72% of patients in the PATHFINDER study (n = 67) and in 75% in the EXPLORER study (n = 12). SAEs were reported in about 40% of those treated in the PATHFINDER study (n = 67) and in just under 42% of those treated in the EXPLORER study (n = 12). However, despite

descriptive similarity in the respective overall rates of AEs, differences of ≥ 10 percentage points between the two studies are frequently evident at the PT and SOC levels, which essentially reveal more adverse events in the EXPLORER study. Possible explanations for these differences in AEs between the studies are an almost twice as long exposure to the study medication and a correspondingly longer safety follow-up in the EXPLORER study compared to the PATHFINDER study. In addition, uncertainties arise in the interpretation of the results of the Explorer study due to the small number of patients (n = 12).

Cognitive effects and intracranial haemorrhage were specified as AESI. AESI of any severity occurred in the cognitive effects category in about 20% of patients, with 3 subjects having a CTCAE grade ≥ 3. Approximately 2% of all patients had an AESI of any severity in the SOC of intracranial haemorrhage. This was a subdural haematoma (PT) in both cases, one of which was reported as an AESI of CTCAE grade ≥ 3, but both as SAEs.

Due to the single-arm study design, a comparative assessment of the data on side effects is not possible.

Overall assessment

The present benefit assessment is based on the results of the pivotal phase II PATHFINDER study and the supportive phase I/II EXPLORER study on mortality, morbidity, health-related quality of life and side effects.

Due to the single-arm study design, a comparative assessment of the data on avapritinib is not possible.

The indirect comparison presented for overall survival in the BLU-285-2405 study is subject to considerable uncertainty. These uncertainties are mainly due to a lack of systematic literature research and evaluation to identify confounders, incomplete adjustment for pre-specified confounders, persistent imbalances after propensity score adjustment, and inadequate handling of missing values, especially for some key covariates defined by the pharmaceutical company. A lack of structural equality of the patient populations cannot be ruled out. Taking into account these uncertainties, the effect estimator for overall survival is not in an order of magnitude to derive an effect with sufficient confidence.

In addition, the indirect comparison by Pilkington et al. (2022) submitted by the pharmaceutical company is not used for the benefit assessment of avapritinib, mainly due to the limited study documents submitted, which do not allow an adequate methodological assessment in the context of the benefit assessment, and due to the conduct of the indirect comparisons on an aggregated (pooled) study level without using complete patient-individual data.

Overall, the indirect comparisons presented are unsuitable for deriving statements about the extent of the additional benefit.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The present benefit assessment is based on the data from the pivotal, single-arm PATHFINDER study and the supportive, single-arm EXPLORER study.

The indirect comparisons presented are not suitable for deriving statements about the extent of the additional benefit.

Since a comparative assessment is therefore not possible, the significance of the evidence is assessed as a hint.

2.1.3 Summary of the assessment

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

Avapritinib (Ayvakyt®) was approved under "exceptional circumstances" as an orphan drug for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL) after at least one prior systemic therapy.

For the benefit assessment, the data of the pivotal, single-arm PATHFINDER study and the supportive EXPLORER study on mortality, morbidity, quality of life and side effects were presented.

In addition, an indirect comparison on overall survival was presented in the BLU-285-2405 study, but this is subject to considerable uncertainty. These uncertainties are mainly due to a lack of systematic literature research and evaluation to identify confounders, incomplete adjustment for pre-specified confounders, persistent imbalances after propensity score adjustment, and inadequate handling of missing values, especially for some key covariates defined by the pharmaceutical company. A lack of structural equality of the patient populations cannot be ruled out. Taking into account these uncertainties, the effect estimator for overall survival is not in an order of magnitude to derive an effect with sufficient confidence.

In addition, the indirect comparison by Pilkington et al. (2022) submitted by the pharmaceutical company is not used for the benefit assessment of avapritinib, mainly due to the limited study documents submitted, which do not allow an adequate methodological assessment in the context of the benefit assessment, and due to the conduct of the indirect comparisons on an aggregated (pooled) study level without using complete patient-individual data.

On the basis of the indirect comparisons presented, it is therefore not possible to make a statement about the extent of the additional benefit.

Since only single-arm data are available and a comparative assessment is not possible, the significance of the evidence is assessed as a hint.

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

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 pharmaceutical company calculated the number of patients in the SHI target population using seven derivation steps.

Based on the data used for the current derivation, which are based on a population from Germany, and based on the comparison of the percentage for AdvSM with another publication from the German healthcare context[2], the number of patients in the range reported by the pharmaceutical company is to be expected.

Uncertainties essentially result from the fact that, with regard to prior systemic therapy, not all OPS codes that can be identified as systemic therapy on the basis of the guideline of the German Society for Haematology and Oncology for the indication of advanced systemic mastocytosis, including off-label use, were included in the submitted routine data analysis with regard to inpatient care. In addition, patients who are in complete remission after systemic therapy or who are currently still on systemic therapy are also included in the target population via the derivation steps applied. It is questionable whether this entire patient group is also eligible for avapritinib.

With regard to the benefit assessment procedure for midostaurin in the therapeutic indication of advanced systemic mastocytosis, it is noticeable that fewer patients are shown among the patient numbers here than in the present procedure for avapritinib, although midostaurin was already assessed in the first line of treatment compared to avapritinib. In this regard, the pharmaceutical company states in the dossier that the derivation of the SHI target population in the procedure for midostaurin was based on international literature data and plausibly explains that the corresponding data are now at least partially considered outdated.

Therefore, the G-BA bases its resolution on the patient numbers provided in the dossier by the pharmaceutical company, which are, however, subject to uncertainties.

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: 1 July 2022):

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

[2] Schwaab J, Cabral do O Hartmann N, Naumann N et al. Importance of Adequate Diagnostic Workup for Correct Diagnosis of Advanced Systemic Mastocytosis. J Allergy Clin Immunol Pract 2020; 8(9): 3121-3127.el. https://dx.doi.org/10.1016/j.jaip.2020.05.005

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

This medicinal product was authorised under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

Avapritinib has been associated with an increased incidence of haemorrhagic events. The risk of intracranial haemorrhage should be carefully assessed before the start of treatment.

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 August 2022).

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 is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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	1 x daily	365	1	365

Consumption:

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.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

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	200 mg	200 mg	1 x 200 mg	365	365 x 200 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 200 mg	30 FCT	€ 22,488.58	€ 1.77	€ 1,283.73	€ 21,203.08
Abbreviations: FCT = film-coated tablets					

LAUER-TAXE® last revised: 15 August 2022

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.

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 31 March 2022, 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, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 July 2022 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 July 2022.

The oral hearing was held on 8 August 2022.

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 6 September 2022, and the proposed resolution was approved.

At its session on 15 September 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation

Subcommittee Medicinal products	22 June 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	2 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2022	Conduct of the oral hearing
Working group Section 35a	16.08.2022; 30 August 2022	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	6 September 2022	Concluding discussion of the draft resolution
Plenum	15 September 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 September 2022

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

Prof. Hecken