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)
Midostaurin (reassessment of an orphan drug after exceeding the 30 million euro threshold: systemic mastocytosis)

of 2 May 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. 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 trials the pharmaceutical company has 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. requirements 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 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 midostaurin (Rydapt) was listed for the first time on 15 October 2017 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. Rydapt for the treatment of aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL) is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

At its session on 5 April 2018, the G-BA approved the benefit assessment of midostaurin in the therapeutic indication "monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL)" 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 Section 5, paragraphs 1 to 6 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.

In a letter dated 1 December 2022, the pharmaceutical company was informed that the EUR 30 million turnover limit for midostaurin had been exceeded within the period from December 2021 to November 2022. By resolution of 2 February 2023 the procedure was suspended till 15 November 2023. By letter dated 2 February 2023, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 15 November 2023, due to exceeding the € 30 million turnover limit. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 6 VerfO on 13 November 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 February 2024 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 midostaurin compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the 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 [1] was not used in the benefit assessment of midostaurin.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to 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 Midostaurin (Rydapt) in accordance with the product information

Rydapt is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).

Therapeutic indication of the resolution (resolution of 2 May 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

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

Appropriate comparator therapy for midostaurin:

Patient-individual therapy with selection of:

- avapritinib (only for subjects after at least one prior systemic therapy and with platelet counts ≥ 50 x 10^9/l),
- cladribine *and*
- imatinib (only for subjects without KIT D816V mutation or with unknown KIT mutational status and for subjects with existing eosinophilia with FIP1L1-PDGFRA fusion gene),

taking into account the general condition, KIT mutational status and prior therapy

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with 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 it determines 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. In this therapeutic indication, avapritinib is the only active ingredient approved alongside midostaurin.

on 2. In principle, allogeneic stem cell transplantation is possible as a non-medicinal treatment option in this therapeutic indication. However, when determining the appropriate comparator therapy, it was assumed that allogeneic stem cell transplantation was not an option at the time of treatment with midostaurin.

on 3. Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

Avapritinib: Resolution of 15.09.2022

Annex VI to Section K of the Pharmaceuticals Directive (last revised: 24.06.2023) Prescribability of approved medicinal products in unapproved 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 (last revised 20.01.2024) 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 generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present

indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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 therapeutic indication according to Section 35a, paragraph 7 SGB V.

The evidence in this therapeutic indication is extremely limited due to the rarity of the mastocytosis disease. The NCCN guideline[2], a written statement from the German Society for Haematology and Medical Oncology (DGHO) and further literature[3,4] on the treatment of mastocytosis are available. Therapy recommendations are based on single-arm studies or retrospective case series according to the available evidence.[5,6,7,8,9,10,11,12]

Midostaurin is the only approved active ingredient for previously untreated patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasia (SM-AHN), or mast cell leukaemia (MCL). According to Section 6, paragraph 2, sentence 2 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. Effects on the medical treatment situation that only result from the addition of the new medicinal product must be disregarded.

Since midostaurin itself is therefore not considered as an appropriate comparator therapy, but in the present case we are dealing with advanced forms of mastocytosis for which cytoreductive treatment is indicated, it is necessary to consider unapproved therapy options in order to implement the appropriate comparator therapy,

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[2] National Comprehensive Cancer Network (NCCN). Systemic Mastocytosis, Version 4.2023 [online]. Plymouth Meeting (USA): NCCN; 2022.

[3] Buonomo A., Nucera E., Criscuolo M. Treatment of indolent and advanced systemic mastocytosis. Mediterr J Hematol Infect Dis 2022, 14(1): e2022040, DOI: http://dx.doi.org/10.4084/MJHID.2022.040

[4] Lee HJ. Recent advances in diagnosis and therapy in systemic mastocytosis. Blood Res. 2023 Apr 30;58(S1):96-108. doi: 10.5045/br.2023.2023024. PMID: 37105564; PMCID: PMC10133845.

[5] Kluin-Nelemans HC, Oldhoff JM, Van Doormaal JJ, et al. Cladribine therapy for systemic mastocytosis. Blood 2003;102:4270-4276.

[6] Lim KH, Pardanani A, Butterfield JH, et al. Cytoreductive therapy in 108 adults with systemic mastocytosis: Outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. Am J Hematol 2009;84:790-794.

[7] Barete S, Lortholary O, Damaj G, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Blood 2015;126:1009-1016.

[8] Heinrich MC, Joensuu H, Demetri GD, et al. Phase II, open-label study evaluating the activity of imatinib in treating life-threatening malignancies known to be associated with imatinib-sensitive tyrosine kinases. Clin Cancer Res 2008;14:2717-2725.

[9] Vega-Ruiz A, Cortes JE, Sever M, et al. Phase II study of imatinib mesylate as therapy for patients with systemic mastocytosis. Leuk Res 2009;33:1481-1484.

[10] Alvarez-Twose I, Matito A, Morgado JM, et al. Imatinib in systemic mastocytosis: a phase IV clinical trial in patients lacking exon 17 KIT mutations and review of the literature. Oncotarget 2017;8:68950-68963.

[11] DeAngelo DJ, Radia DH, George TI, et al. Safety and efficacy of avapritinib in advanced systemic mastocytosis: The phase 1 EXPLORER trial. Nat Med 2021;27:2183-2191.

[12] Gotlib J, Reiter A, Radia DH, et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: Interim analysis of the phase 2 PATHFINDER trial. Nat Med 2021;27:2192-2199.

particularly for previously untreated patients. According to the generally recognised state of medical knowledge in the therapeutic indication to be assessed, the off-label use is considered to be the therapy standard as it would be without midostaurin (Section 6, paragraph 2, sentence 3, number 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV)).

Cladribine is an evidence-based, relevant therapy option for patients when, for example, a rapid reduction in disease burden is required. Imatinib is an evidence-based relevant therapy option for subjects without a KIT D816V mutation or with unknown KIT mutational status and for subjects with eosinophilia with FIP1L1-PDGFRA fusion gene.

Avapritinib is also approved for patients who have undergone at least one prior therapy. According to guideline recommendations and the product information for avapritinib, treatment is not recommended for patients with a platelet count < 50 × 10^9/l.

In accordance with the generally recognised state of medical knowledge, it must be established in the overall assessment that the off-label use of the above-mentioned therapy options is generally preferable to the medicinal products previously approved in the therapeutic indication in the context of patient-individual therapy, taking into account the general condition, the KIT mutational status and the prior therapy for relevant patient groups or indication areas; Section 6, paragraph 2, sentence 3, number 3 AM-NutzenV.

For the present resolution, the G-BA therefore determines a patient-individual therapy with selection of avapritinib, cladribine and imatinib, taking into account the patient's general condition, KIT mutational status and prior therapy.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of midostaurin for the treatment of adults with ASM, SM-AHN or MCL, the pharmaceutical company presents data from the pivotal single-

arm phase II CPKC412D2201 and CPKC412A2213 studies as well as a non-randomised comparison by Lübke et al., 2022[13].

CPKC412D2201 study and CPKC412A2213 study

The CPKC412D2201 and CPKC412A2213 studies are single-arm phase II studies.

The CPKC412D2201 study enrolled 116 patients with aggressive systemic mastocytosis or mast cell leukaemia who met the WHO diagnostic criteria and had at least one measurable Cfinding.

The enrolled patients received midostaurin therapy continuously until death, disease progression or occurrence of unacceptable toxicity. The primary endpoint of the study was objective response rate.

The CPKC412A2213 study enrolled 26 patients with histologically proven ASM or MCL.

The patients were also treated daily with midostaurin. The maximum treatment duration was 12 cycles of 28 days each. Treatment was discontinued in the absence of any response to therapy after 2 cycles. The primary endpoint of the study was objective response rate.

Due to the single-arm study design, the CPKC412D2001 and CPKC412A2213 studies presented by the pharmaceutical company do not allow a comparison with the appropriate comparator therapy and are therefore unsuitable for the assessment of an additional benefit of midostaurin compared with the appropriate comparator therapy.

Lübke 2022 study

The publication by Lübke et al, 2022 describes a retrospective, non-randomised comparator study using data from the German Registry of the Diseases of Eosinophils and Mast Cells. The study enrolled 139 patients with advanced systemic mastocytosis who were enrolled in the registry between 2003 and 2020.

Patients were treated with midostaurin or cladribine as monotherapy or with sequential administration of both active ingredients. The dosage of midostaurin was in accordance with the product information. Cladribine was used in accordance with the guideline recommendations.

In the registry study, all patients in the comparator arm were treated exclusively with cladribine. There was no patient-individual therapy with selection of cladribine, avapritinib or imatinib, taking into account the general condition, the KIT mutational status and the prior therapy in accordance with the appropriate comparator therapy defined by the G-BA. It is not clear from the data in the publication whether the patient population analysed are those patients for whom cladribine is the appropriate patient-individual comparator therapy.

A propensity score analysis was performed to account for differences in patient characteristics in the non-randomised study. However, the procedure was not sufficiently described either in the dossier or in the publication. There is a lack of information on the identification and completeness of the confounders and detailed information on the adjustment methodology

[13] Lubke J, Schwaab J, Naumann N et al. Superior Efficacy of Midostaurin Over Cladribine in Advanced Systemic Mastocytosis: A Registry-Based Analysis. J Clin Oncol 2022; 40(16): 1783-1794. https://doi.org/10.1200/JCO.21.01849.

used. During the oral hearing, the pharmaceutical company stated that it did not have access to the detailed study documents, as the non-randomised comparison was conducted independently of the pharmaceutical company. However, this leaves key methodological aspects unclear for the benefit assessment, so that it is not possible to assess whether the methodology used for the indirect comparison is appropriate.

Due to the lack of implementation of the appropriate comparator therapy and, in particular, the lack of detailed information on the methodology of the non-randomised comparison, the publication by Lübke et al. was not used for the benefit assessment.

Overall assessment

The results of the single-arm CPKC412D2201 and CPKC412A2213 studies as well as the non-randomised comparison by Lübke from 2022 are available for the assessment of the additional benefit of midostaurin.

The results of the single-arm CPK412D2201 and CPK412A2213 studies presented are unsuitable for assessment of the additional benefit as they do not allow a comparison with the appropriate comparator therapy.

The results of the non-randomised comparison by Lübke are also not used for the benefit assessment due to the lack of detailed information on the methodology and the lack of implementation of the appropriate comparator therapy.

Overall, no suitable data are therefore available for an assessment of the additional benefit of midostaurin. Thus, an additional benefit of midostaurin for adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL) compared to the appropriate comparator therapy is not proven.

2.1.4 Summary of the assessment

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

"Rydapt is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL)"

For the benefit assessment of midostaurin, the pharmaceutical company presented the results of the single-arm phase II CPKC412D2201 and CPKC412A2213 studies as well as the non-randomised comparison by Lübke et al., 2022.

For the non-randomised comparison, there is a lack of relevant information on the methodology used. Furthermore, the data presented are unsuitable for a comparison with the appropriate comparator therapy.

An additional benefit of midostaurin as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL) compared to the appropriate comparator therapy is therefore not proven.

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

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

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

On the one hand, there are uncertainties regarding the lower limit of prevalence with regard to the survey of patients with systemic mastocytosis and the possible inclusion of patients with indolent mastocytosis. In addition, uncertainties arise because the prevalence in children and adolescents is lower than in adults, but the pharmaceutical company transfers the prevalence in relation to patients aged 15 years of age and over to the entire SHI population. With regard to the upper limit of prevalence, it is unclear to what extent the underlying data can be applied to the entire SHI population.

Furthermore, the calculation of patient numbers does not take into account the fact that cytoreductive therapy must be indicated for patients for whom midostaurin is indicated and that stem cell transplantation is not an option at the time of therapy.

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 Rydapt (active ingredient: midostaurin) at the following publicly accessible link (last access: 25 March 2024):

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

Treatment with midostaurin should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasm and mast cell leukaemia.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

For the cost representation, one year is assumed for all medicinal products. 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.

There are no marketing authorisations for cladribine and imatinib for this therapeutic indication. The G-BA uses the therapy protocols from the recommendations of the German

Society for Haematology and Medical Oncology (DGHO) as the basis for cost calculation in the context of the off-label use of this therapy. [14,15]

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				
Midostaurin	Continuous, 2 x daily	730	1	365
Appropriate comparator therapy				
Avapritinib	Continuous, 1 x daily	365	1	365
Cladribine	Day 1 - 5: 28-day cycle	3 - 6	5	15 - 30
Imatinib	Continuous, 1 x daily	365	1	365

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1,72 m; average body weight: 77.7 kg).[16]

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					
Midostaurin	100 mg	200 mg	8 x 25 mg	365	2,920 x 25 mg

[14] Reiter A, Jawhar M, Balabanov S et al. Onkopedia Leitlinien - Mastozytose, systemische [online]. 2020. URL: https://www.onkopedia.com/de/onkopedia/guidelines/mastozytose-systemische/@@guideline/html/index.html

[15] Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology). Onkopedia Leitlinien - Mastozytose, systemische - Therapieprotokolle [online]. 2020. URL: https://www.onkopedia.com/de/onkopedia/addendums/mastozytose-systemische-therapieprotokolle/@@guideline/html/index.html

[16] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Avapritinib	200 mg	200 mg	1 x 200 mg	365	365 x 200 mg
Cladribine	0.14 mg/kg	10.78 mg	2 x 10 mg	15 - 30	30 - 60 x 10 mg
Imatinib	400 mg	400 mg	1 x 400 mg	365	365 x 400 mg

Costs:

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

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					
Midostaurin 25 mg	4 x 28 SC	€ 15,991.76	€ 2.00	€ 910.00	€ 15,079.76
Appropriate comparator therapy					
Avapritinib 200 mg	30 FCT	€ 20,466.13	€ 2.00	€ 1,168.23	€ 19,295.90
Cladribine 10 mg	5 SFI	€ 2,006.52	€ 2.00	€ 254.40	€ 1,750.12
Imatinib 400 mg[17]	90 FCT	€ 538.33	€ 2.00	€ 41.68	€ 494.65
Abbreviations: FCT = film-coated tablets; SFI = solution for injection; SC = soft capsules					

LAUER-TAXE® last revised: 15 April 2024

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate

[17] Fixed reimbursement rate

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 need to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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

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

Basic principles of the assessed medicinal product

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

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication)

and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

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

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

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

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

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

Concomitant active ingredient

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

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

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

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

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

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

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

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

Designation

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

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

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to

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

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

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

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

References:
Product information for midostaurin (Rydapt); product information for Rydapt® 25 mg soft capsules; last revised: June 2023

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 its session on 20 December 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

Against the background of the legal requirements introduced with the ALBVVG (Act to Combat Supply Shortages and Improve the Supply of Medicines) for the determination of the off-label use of medicinal products by way of exception, the appropriate comparator therapy was reviewed and newly implemented on 28 November 2023.

On 13 November 2023, the pharmaceutical company submitted a dossier for the benefit assessment of midostaurin to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 14 November 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 midostaurin.

The dossier assessment by the IQWiG was submitted to the G-BA on 9 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 February 2024. The deadline for submitting statements was 7 March 2024.

The oral hearing was held on 25 March 2024.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 23 April 2024, and the proposed resolution was approved.

At its session on 2 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	20 December 2022	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	28 November 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	20 March 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	25 March 2024	Conduct of the oral hearing
Working group Section 35a	4 March 2024 17 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	23 April 2024	Concluding discussion of the draft resolution
Plenum	2 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 2 May 2024

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

Prof. Hecken