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: Ripretinib (gastrointestinal stromal tumours (GIST), ≥ 3 prior therapies)

of 16 June 2022

Contents

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of 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), the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

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

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect 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

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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 relevant date for the first placing on the (German) market of the active ingredient ripretinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 January 2022. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 23 December 2021.

Ripretinib indicated for the treatment of advanced gastrointestinal stromal tumour (GIST) is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 April 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 made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G22-02) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has 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 ripretinib.

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

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2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Ripretinib (Qinlock) in accordance with the product information

QINLOCK is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

Therapeutic indication of the resolution (resolution of 16 June 2022):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Adults with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib

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

Hint for a major additional benefit

Justification:

The benefit assessment is based on the results of the randomised, double-blind, placebo-controlled phase III INVICTUS study. In the study, ripretinib in combination with best supportive care (BSC) is compared to placebo and BSC (hereafter: ripretinib versus placebo).

Adults with advanced gastrointestinal stromal tumour (GIST) who received at least three kinase inhibitors (imatinib, sunitinib and regorafenib) were enrolled.

A total of 129 patients were randomised in a 2:1 ratio to the two treatment arms (test arm: N = 85, control arm: N = 44). Stratification was by number of prior therapies (3 vs ≥ 4) and Eastern Cooperative Oncology Group - Performance Status (ECOG-PS; 0 vs 1 or 2).

Patient characteristics were largely balanced between the two study arms, but study participants in the placebo arm were a median of 5.5 years older than those in the ripretinib arm. In addition, the study participants differed with regard to the location of the primary tumour and the histology at initial diagnosis. According to the statements of the clinical experts within the framework of the written statement procedure, these factors - age, primary localisation at the time of initial diagnosis, mutational status - do not play a predictive role in the present treatment setting, so that the imbalances that occurred have no relevance for the analysis and the significance of the study from a clinical point of view.

Treatment in both arms was carried out in a double-blind phase until disease progression according to mRECIST criteria (modified Response Evaluation Criteria in Solid Tumours Version 1.1; GIST-specific), after which the patients were transferred to an open-label phase.

In the closed-label phase, the treatment in the test arm was 150 mg ripretinib 1 x daily according to the product information. The administration form, appearance and intake of the placebo preparation in the control arm were identical to the test intervention. However, there

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is no information available on what BSC refers to. After disease progression, the study participants were transferred to an open-label phase. The following options were available to patients from the test arm after consultation with the principal investigator: a dose increase (2 x 150 mg daily), continued treatment at the same dose or discontinuation of the study medication. Study participants in the control arm could choose between switching to the test arm (150 mg ripretinib, 1 x daily) and discontinuing study medication; in the event of further disease progression, they had the same options available to them as patients in the ripretinib arm after disease progression.

The INVICTUS study was conducted at 29 study sites in 12 countries (USA, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Poland, Singapore, Spain and the UK). The study was launched in February 2018 and is currently ongoing. Currently, three data cut-offs are available. The data cut-off from 31 May 2019 is a primary analysis specified a priori for the primary endpoint of progression-free survival. The 2nd data cut-off from 10 August 2020 was requested by the EMA and forms the basis of this benefit assessment. The third data cut-off from 15 January 2021 is an ad hoc data cut-off initiated for a congress.

Mortality

The overall survival is defined in the INVICTUS study as the time between randomisation and death from any cause.

The overall survival analyses are based on the ITT population, which means that patients from the control arm, who switched to the test arm after disease progression or patients who received a dose increase, were also enrolled.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of ripretinib versus placebo.

The extent of the prolongation achieved in overall survival is assessed as a very significant improvement.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the INVICTUS study. It is operationalised as the time (in weeks) from randomisation to the first proven disease progression or death from any cause.

Prolongation of PFS is statistically significantly with ripretinib compared to placebo.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is assessed according to RECIST V1.1 criteria (modified by GIST) and thus, not in a symptom-related manner but by means of laboratory parametric, imaging, and haematological procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

Symptomatology (EORTC QLQ-C30)

Disease symptomatology was assessed in the INVICTUS study using the cancer-specific questionnaire EORTC QLQ-C30. The pharmaceutical company submitted responder analyses

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for the percentage of patients with a change of ≥ 10 points or 15% of the scale range for the time to 1st deterioration.

However, the analyses refer exclusively to the ITT population in the double-blind phase and thus, not to the open-label phase. However, according to the study protocol, the EORTC QLQ-C30 was also collected after cross-over until the end of treatment.

With its written statement, the pharmaceutical company submitted evaluations for the time to 1st deterioration over the entire study period. These evaluations are used for the present assessment despite uncertainties. The uncertainties are based in particular on unclear follow-up until the end of the study, the large differences in return rates between the two study arms, and the cross-over and unblinding of study participants. According to the study protocol, patient-reported endpoints were collected throughout the study period until the end of treatment. However, it is unclear how many patients who discontinued the study after disease progression (especially in the ripretinib arm) were no longer assessed. In addition, at the beginning of cycles 3 and 6 and from cycle 12 onwards, the difference in return rate between the treatment groups is > 15%. In case of progression, patients could switch from the placebo to the ripretinib arm, with unblinding. Unblinding also occurred for patients in the ripretinib arm who continued treatment after progression. Moreover, the reasons for censorship are not known in every case.

In the stratified analysis of time to first deterioration by ≥ 10 points, there is no statistically significant difference between the treatment arms for any of the endpoints, so there are neither advantages nor disadvantages for ripretinib compared to placebo.

Health status (EQ-5D VAS)

The health status is assessed in the INVICTUS study using the EQ-5D visual analogue scale (VAS). The pharmaceutical company submitted responder analysis, operationalised as time to 1st deterioration with a change of ≥ 15 points.

Taking into account the explanations in the "Symptomatology" section, the evaluations on the health status submitted by the pharmaceutical company within the framework of the written statement procedure are used for the present benefit assessment, based on the time to 1st deterioration over the entire study period.

For health status assessed by EQ-5D VAS, there was a statically significant difference to the advantage of ripretinib compared to placebo. However, the same uncertainties remain that are already listed in the Symptomatology section.

In the overall assessment of the endpoint category morbidity, there were neither advantages nor disadvantages for ripretinib compared to placebo in the assessed symptomatology. The endpoint of health status shows a positive effect for the treatment with ripretinib. Taking into account the present advanced stage of disease and treatment, as well as the magnitude of the effect, a benefit for ripretinib in health status is observed despite the uncertainties present.

Quality of life

In the INVICTUS study, health-related quality of life was assessed using the functional scales and the global health status scale (overall assessment) of the cancer-specific questionnaire EORTC QLQ-C30. The pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 10 points or ≥ 15% of the scale range for the time to 1st deterioration.

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Taking into account the explanations in the "Symptomatology" section, the evaluations on the quality of life submitted by the pharmaceutical company within the framework of the written statement procedure are used for the present benefit assessment, based on the time to 1st deterioration over the entire study period.

In the stratified analysis of the time to the first deterioration by ≥ 10 points, there is no statistically significant difference between the treatment arms for the endpoints of cognitive functioning, emotional functioning and social functioning.

Regarding the endpoints of physical functioning and role functioning, there is a statistically significant difference in the benefit of ripretinib versus placebo.

For the endpoint of global health status, however, there is a statically significant difference to the disadvantage of ripretinib versus placebo. Compared to the other endpoints of the EORTC QLQ-C30, few events occurred for this endpoint and a high percentage (77.3%) of patients in the placebo arm were censored. The reasons for censoring were not given. Against the background of an acceptable return rate and numerous deaths in the placebo arm, it is assumed that a large percentage of patients died before the response threshold was reached. For this reason, no conclusions are derived from the result on global health status for the assessment of health-related quality of life.

Uncertainties remain, which have already been discussed in the symptomatology section.

Overall, for the endpoint category of quality of life, two positive effects are shown for ripretinib for the endpoints of physical functioning and role functioning, which are considered to be significant, taking into account the present advanced stage of disease and treatment and the magnitude of the effects shown, despite uncertainties.

Side effects

The evaluation of the results on side effects is based on the double-blind phase of the safety population. All endpoints in the AE category are collected up to 30 days after the last administration of study medication.

Adverse events (AEs) were reported by almost all subjects in the ripretinib arm (98.8%) and the placebo arm (97.7%). Severe AEs (CTCAE grade ≥ 3) occurred in 55.3% of subjects in the ripretinib arm and in 51.2% in the placebo arm. Serious adverse events (SAEs) occurred in 34.1% of subjects in the ripretinib arm, 44.2% in the placebo arm. AEs leading to therapy discontinuation occurred in 7 subjects (8.2%) in the ripretinib arm and 5 people (11.6%) in the placebo arm.

Time-to-event analyses calculated post hoc were presented by the pharmaceutical company in the dossier. These show a statistically significant difference in favour of ripretinib compared to placebo for the endpoints of severe AEs and serious AEs. For the endpoint of discontinuation due to AEs, there is no statistically significant difference.

Against the background of different treatment and observation periods between the study arms, time-to-event analyses are basically adequate evaluations. If adverse events that represent disease-related events (e.g., progression, exacerbation) are included in the AE assessment and thus, also in the evaluation, additional AE analyses should be conducted for the overall rates (AE, severe AE and SAE) in which these events are not taken into account. With regard to the advanced stage of the disease, it can be assumed that progression events or events that correspond to the symptomatology of the underlying disease were also recorded to a relevant extent in both study arms and were included in the evaluations of the

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AEs. In this situation, in particular, additional AE analyses are required that do not take these events into account.

The pharmaceutical company did not submit any corresponding analyses in the dossier. In its written statement, the pharmaceutical company presents further analyses of the adverse events, excluding events of SOC "Neoplasms benign, malignant and unspecified (including cysts and polyps)" as an approximation. Further symptoms or events that could be due to progression of the underlying disease are not discussed by the pharmaceutical company. In the view of the G-BA, the selected procedure is not suitable to adequately exclude progression events from the side effects.

For these reasons, there are great uncertainties with regard to the interpretation of the results on the basis of the evaluations on the AEs presented. Taking into account that this is a comparison of an active, targeted anti-tumour therapy compared to placebo and in view of fewer patients who discontinued therapy due to AEs, an overall advantage in the therapeutic benefit with regard to the side effects of ripretinib is assumed. Against this background, a quantification of the present results in the endpoint category of side effects for the extent of additional benefit is not possible; the results can only be interpreted to a limited extent.

Overall assessment / conclusion

For the benefit assessment of ripretinib for the treatment of adults with advanced gastrointestinal stromal tumour (GIST) who have previously received treatment with three or more kinase inhibitors, including imatinib, data on mortality, morbidity, quality of life and side effects are available from the INVICTUS study.

For the endpoint of overall survival, there was a statistically significant difference in favour of ripretinib in combination with best supportive care (BSC) versus placebo in combination with BSC. The magnitude of the effect is assessed as a very significant improvement.

In the overall assessment of the endpoint category morbidity, there were neither advantages nor disadvantages for ripretinib compared to placebo in the assessed symptomatology. In contrast, the endpoint of health status shows a clear advantage for the treatment with ripretinib.

For the endpoint category of quality of life, there are clear advantages in the endpoints of physical functioning and role functioning.

Taking into account the advanced stage of disease and treatment and the magnitude of these effects, the benefits in morbidity and health-related quality of life are considered to be significant despite the uncertainties.

With regard to side effects, there are major uncertainties in relation to the evaluations on adverse events (AEs) presented. In view of the advanced stage of the disease, it can be assumed that progression events or events that correspond to the symptomatology of the underlying disease were also recorded to a relevant extent in both study arms and included in the evaluations of the AEs. Appropriate additional AE analyses disregarding these events were not submitted by the pharmaceutical company.

Taking into account that this is a comparison of an active, targeted anti-tumour therapy versus placebo and in view of fewer patients who discontinued therapy due to AEs, the overall side effect profile of ripretinib is assumed to be advantageous. Against this background, a quantification of the present results in the endpoint category of side effects for the extent of additional benefit is not possible.

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In the overall assessment, the G-BA comes to the conclusion that, due to the extent of the prolongation of survival and in view of the available results on the patient-reported endpoints of health status, physical functioning and role functioning as well as on the endpoints of severe AEs and SAEs, which support the overall additional benefit, a previously unattained major improvement in the therapy-relevant benefit in the therapeutic indication is established for ripretinib, particularly against the background of the advanced line of therapy and the associated poor prognosis of the patients.

The overall assessment identifies a major additional benefit for ripretinib in adults with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

Significance of the evidence

The present benefit assessment is based on the results of the ongoing randomised, multicentre phase III INVICTUS study.

At study level, a low risk of bias can generally be assumed for the double-blind phase.

For the open-label phase (after progression), a high risk of bias can be assumed, among other things due to the possible cross-over. In addition, the certainty of the results for all endpoints is classified as limited based on the respective high risk of bias:

Patients in the placebo arm had the option to switch to the ripretinib arm after disease progression, therefore the effect of ripretinib on overall survival is prone to risk of bias.

The results on the patient-reported endpoints of morbidity and health-related quality of life are prone to risk of bias due to relevant uncertainties, especially in the follow-up until the end of the study, large differences in return rates between the two study arms, as well as cross-over and unblinding of study participants after progression. Moreover, the reasons for censorship are not known in every case.

The results on side effects also include events due to progression and symptomatology of the underlying disease, so these should be considered as being prone to a high risk of bias.

In summary, the G-BA deduces a hint for the identified additional benefit with regard to the reliability of data (probability of additional benefit).

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Qinlock with the active ingredient ripretinib.

Ripretinib is approved for the treatment of adults with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

The assessment is based on the randomised, multicentre phase III INVICTUS study, which investigated ripretinib in combination with best supportive care (BSC) versus placebo and BSC. The study was double-blind until progression, and open-label thereafter.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of ripretinib. The magnitude of the effect is assessed as a very significant improvement.

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In the overall assessment of morbidity, the endpoint of health status shows a clear advantage for treatment with ripretinib over placebo. There were neither advantages nor disadvantages for ripretinib compared to placebo in the symptomatology assessed.

For quality of life, there are clear advantages in the endpoints of physical functioning and role functioning.

Taking into account the advanced stage of disease and treatment and the magnitude of these effects, the benefits in morbidity and health-related quality of life are considered to be significant despite the uncertainties.

With regard to side effects, there are major uncertainties in relation to the evaluations on adverse events (AEs) presented. In view of the advanced stage of the disease, it can be assumed that progression events or events that correspond to the symptomatology of the underlying disease were also recorded to a relevant extent in both study arms and included in the evaluations of the AEs. Appropriate additional AE analyses disregarding these events were not submitted by the pharmaceutical company.

Taking into account that this is a comparison of an active, targeted anti-tumour therapy versus placebo and in view of fewer patients who discontinued therapy due to AEs, the overall side effect profile of ripretinib is assumed to be advantageous. Against this background, a quantification of the present results in the endpoint category of side effects for the extent of additional benefit is not possible.

In the overall assessment, the G-BA comes to the conclusion that, due to the extent of the prolongation of survival and in view of the available results on the patient-reported endpoints of health status, physical functioning and role functioning, which support the overall additional benefit, a previously unattained major improvement in the therapy-relevant benefit in the therapeutic indication is established for ripretinib, particularly against the background of the advanced lines of therapy and the associated poor prognosis of the patients.

The overall assessment identifies a major additional benefit for ripretinib in adults with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

The reliability of data of the additional benefit identified is classified as a hint.

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

Adults with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib

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

The pharmaceutical company's data on the number of patients in the SHI target population are uncertain due to the limitations. In particular, the upper limit given is potentially underestimated, also compared to previous procedures in other lines of therapy (regorafenib, avapritinib). This underestimation is partly due to the fact that patients showing disease progression were not sufficiently considered in the calculation of the target population. Nevertheless, in the absence of better data basis, the patient numbers submitted by the pharmaceutical company in the dossier are used.

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2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Qinlock (active ingredient: ripretinib) at the following publicly accessible link (last access: 12 January 2022):

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

Treatment with ripretinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, internal medicine and gastroenterology, and other specialists participating in the Oncology Agreement all of whom are experienced in the treatment of patients with gastrointestinal stromal tumours (GIST).

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 June 2022).

According to the product information of ripretinib, a ripretinib dose of 150 mg once daily is recommended in the present therapeutic indication for as long as benefit is observed or until unacceptable toxicity occurs.

For the presentation of the costs, one year is assumed for all medicinal products. This does not take into account the fact that treatment may be discontinued prematurely due to non-response or intolerance. The discontinuation criteria according to the product information of the individual active ingredients must be taken into account when using the medicinal products.

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.

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				
Ripretinib	1 x daily	365	1	365

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Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ripretinib	150 mg (= 3 tablets)	150 mg	3 x 50 mg	365	1095 x 50 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					
Ripretinib	90 TAB	€ 26,410.17	€ 1.77	€ 1,505.00	€ 24,903.40
Abbreviations: TAB = Tablets					

LAUER-TAXE® last revised: 1 June 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.

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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 23 December 2021, the pharmaceutical company submitted a dossier for the benefit assessment of ripretinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 April 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 April 2022.

The oral hearing was held on 9 May 2022.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 25 May 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 were discussed at the session of the subcommittee on 8 June 2022, and the draft resolution was approved.

At its session on 16 June 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	29 March 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	4 May 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 May 2022	Conduct of the oral hearing
Working group Section 35a	18 May 2022 1 June 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

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Subcommittee Medicinal products	8 June 2022	Concluding discussion of the draft resolution
Plenum	16 June 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 June 2022

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

Prof. Hecken

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