Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Neratinib (Breast Cancer, HR-Positive, HER2-Positive, Adjuvant Treatment)

of 14 May 2020

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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient neratinib 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 December 2019. 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 28 November 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 March 2020, 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 neratinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assessed 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 neratinib.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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 neratinib (Nerlynx ®) in accordance with product information

Nerlynx is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

For the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago

Appropriate comparator therapy:

Monitoring wait-and-see approach

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. According to the authorisation status, the active ingredients tamoxifen, anastrozole, letrozole, exemestan, leuprorelin, goserelin, cyclophosphamide, docetaxel, doxorubicin,

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

epirubicin, 5-fluorouracil, methotrexate, paclitaxel, pertuzumab, trastuzumab and vincristine are available for the treatment of hormone receptor-positive and HER2-overexpressed/amplified early-stage breast cancer.

The marketing authorisation of trastuzumab covers its use in combination with docetaxel and carboplatin for adjuvant chemotherapy. In other constellations, carboplatin is not approved for use in adjuvant treatment.

On 2. A non-medicinal treatment is not considered for this therapeutic indication.

On 3. The following resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V is available:

- Pertuzumab: Resolution of 20 December 2018 (limited until 2 January 2022)

On 4. The generally accepted state of medical knowledge was illustrated by research for guidelines as well as systematic reviews of clinical studies in this indication.

In the benefit assessment according to Section 35a SGB V, the active ingredient pertuzumab in adjuvant treatment was assessed. In the benefit assessment, pertuzumab + trastuzumab + chemotherapy showed a hint for a minor additional benefit compared with trastuzumab + chemotherapy (resolution of 20 December 2018). The resolution was limited to 2 January 2022, in particular because of outstanding data on overall survival and relapses.

For the extended adjuvant therapy after completion of trastuzumab-based therapy, there are currently no treatment recommendations that could serve as appropriate comparator therapy for neratinib. For this therapy situation according to the approved therapeutic indication, a monitoring wait-and-see approach was therefore determined as an appropriate comparator therapy.

Adjuvant chemotherapy, radiotherapy, or endocrine therapy is not part of the appropriate comparator therapy; the use as a patient-individual therapy option remains unaffected. Because the patients have a positive hormone receptor status, it is assumed that they will also receive endocrine therapy.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of neratinib is assessed as follows.

For neratinib for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago, there is a hint for a minor additional benefit.

Justification:

The benefit assessment of neratinib is based on results of the pivotal, randomised, double-blind Phase III ExteNET study. This is an ongoing, international, multi-centre study that was conducted in 39 countries and 476 study centres.

The study included adult patients with HER2-overexpressed/amplified, fully resected, histologically confirmed early-stage breast cancer who had previously received both (neo)adjuvant chemotherapy and treatment with trastuzumab. In the study, patients should have had a tumour stage of I–IIIc in accordance with the American Joint Committee on Cancer (AJCC).

The 2840 patients included in the study were randomised to the neratinib arm (N = 1420) or placebo arm (N = 1420) at a ratio of 1:1. Randomisation was stratified by hormone receptor status (positive/negative), the nodal status (0/1–3/≥ 4) and the method of administration of the previous trastuzumab therapy (concurrent with chemotherapy/sequential to chemotherapy).

Based on the investigation regime carried out in the study, the placebo comparison up to the first data cut-off is regarded as a sufficient approximation to the appropriate comparator therapy, a monitoring wait-and-see approach.

The patients had a median age of 51 years at the time of inclusion and were estimated to be in the second year after primary treatment at the time of randomisation.

Study participants were treated with neratinib or placebo for one year or until a relapse or other termination criterion (patient decision, adverse events [AEs], protocol violation, or death).

In accordance with the original study protocol, patients were to be followed for up to five years. In the course of protocol changes, the follow-up period was reduced from five to two years after randomisation, and the collection of patient-reported endpoints on health status and health-related quality of life was discontinued. Another later protocol change extended the follow-up to five years after randomisation for the relapse endpoint and until the last patient included died for the overall survival endpoint. Because of the discontinuation and resumption of the follow-up, the patients had to agree to participate in the study again. A considerable proportion of the patients did not agree to participate again. Furthermore, these endpoints were collected from patient records and no longer within an investigation scheme within the study.

In the dossier, the pharmaceutical company submits results for the sub-population of hormone receptor-positive patients regardless of the time between completion of trastuzumab treatment and randomisation. According to the approved therapeutic indication of neratinib, the results of the sub-population of hormone receptor-positive patients whose treatment with trastuzumab has been completed for less than one year shall be used for the assessment.

A total of three data cut-offs are available for the study. For the benefit assessment, the first data cut-off of 7 July 2014 was used. This is the pre-specified primary analysis for the two-year period after randomisation. Later data cut-offs are not usable because after discontinuation and resumption of the follow-up observation, the structural equality between the treatment arms can no longer be guaranteed, and the appropriate comparator therapy can be regarded as not implemented. Regular examinations were no longer planned within the study. Moreover, in a high proportion of patients, the examination intervals were significantly longer than recommended in the guidelines.

Extent and probability of the additional benefit

Mortality

Overall survival

In the ExteNET study, overall survival is defined as the time from randomisation to death of any cause.

In accordance with the study protocol, overall survival should not be evaluated until the 248th death. Because this number was not reached for the relevant data cut-off and for no other data cut-off beyond that, no evaluations are available for the overall survival endpoint for the relevant sub-population.

As the time of the first data cut-off, in the sub-population of hormone receptor-positive patients, nine deaths in the intervention arm and 14 deaths in the comparator arm occurred (regardless of the time from completion of trastuzumab therapy to randomisation).

Morbidity

Relapses

Patients in this therapeutic indication are treated with a curative therapy approach as part of the extended adjuvant treatment of breast cancer after complete resection, (neo)adjuvant chemotherapy, and trastuzumab treatment. Nevertheless, tumour cells can remain and cause a relapse in the further course. A relapse means that the attempt to cure the disease with the curative therapy approach was not successful. The occurrence of a relapse is patient-relevant.

The endpoint relapse (operationalised as relapse rate and relapse-free survival) comprises the following individual components:

- ductal carcinoma in situ
- invasive ipsilateral relapse of the breast
- invasive contralateral breast cancer
- local/regional invasive relapse
- remote metastases (including death because of breast cancer)
- death by any cause

The endpoint relapses operationalised as relapse rate describes the proportion of patients with a relapse event or death at the corresponding data cut-off (event rate). In the endpoint relapses operationalised as relapse-free survival, the time to the event (relapse or death) is also considered (event time analysis). The median observation period for the data cut-off used is 24 months. Taking into account the previous treatment with trastuzumab and the time between trastuzumab treatment and randomisation, the patients were estimated to be in the fourth year after primary treatment at the time of analysis.

Relapse rate (event rate)

For the relapse rate, there is a statistically significant difference to the advantage of neratinib compared with placebo (relative risk [RR]: 0.43 [95% CI: 0.27; 0.67]; $p < 0.001$). At the time of the data cut-off, 3.9% of patients in the neratinib arm and 9.0% of patients in the placebo arm had experienced a relapse.

Missing values (19.1% in the intervention arm; 12.8% in the control arm) were replaced by a last-observation-carried-forward (LOCF) analysis. For patients who had not experienced a relapse at the end of their observation period, it was assumed that no relapse had occurred at the time of analysis. Sensitivity analyses were carried out in order to estimate the robustness of the effect with regard to the missing values. These conservative sensitivity analyses, which

included replacing missing values in the intervention arm in accordance the risk of relapse in the control group, confirm the existing positive effect of neratinib compared with placebo.

Relapse-free survival (event time analyses)

In terms of relapse-free survival, there is a statistically significant difference to the benefit of neratinib compared with placebo (hazard ratio [HR]: 0.45 [95% CI: 0.28; 0.71]; $p < 0.001$). In both the neratinib and placebo arm, the median time to the event was not yet reached.

Overall, there is a clear, clinically relevant advantage of neratinib in terms of the endpoint relapses (operationalised as relapse rate and relapse-free survival) compared with a monitoring wait-and-see approach.

Health status (EQ-5D VAS)

In the ExteNET study, health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the benefit assessment, the pharmaceutical company submitted evaluations of the mean difference compared with the benefit assessment based on an analysis with mixed models for repeated measurements (MMRM). There is no statistically significant difference between the treatment groups for the mean change at month 12.

Quality of life

In the study, health-related quality of life is surveyed using the disease-specific FACT-B[2] questionnaire. The FACT-B questionnaire consists of the cross-tumour disease questionnaire (FACT-G) and a breast cancer specific sub-scale (BCS). The FACT-G questionnaire consists of the four sub-scales physical well-being (PWB), emotional well-being (EWB), functional well-being (FWB), and social well-being (SWB). For the sub-scales of the FACT-B questionnaire, only results of the BCS are available for the relevant sub-population. Only the FACT-B total score was considered in the assessment of the additional benefit because this provides a comprehensive overview of the data on patients' health-related quality of life. The individual sub-scales of the FACT-B are therefore presented only on a supplementary basis.

For the benefit assessment, the pharmaceutical company submitted evaluations of the mean difference compared with the baseline based on an MMRM analysis for this questionnaire. In the total score of the FACT-B, there is no statistically significant difference between the treatment groups for the mean change at month 12.

Side effects

AEs overall

By the time of the first data cut-off, 98.0% of patients in the neratinib arm and 86.3% of patients in the control arm had experienced an adverse event. The results are only presented as a supplement.

Serious adverse events (SAEs)

In terms of serious adverse events, there is a statistically significant difference to the disadvantage of neratinib compared with placebo. In both the intervention and the control arm, the median time to the event was not yet achieved.

Severe adverse events (CTCAE grade ≥ 3)

In terms of severe adverse events (CTCAE grade ≥ 3), there is a statistically significant difference to the disadvantage of neratinib compared with placebo. Severe adverse events (CTCAE grade ≥ 3) occur after 8.6 months (median) under treatment with neratinib. In the control arm, the median time to the event was not yet reached.

[2] Functional Assessment of Cancer Therapy – Breast

Therapy discontinuations because of AEs

In terms of therapy discontinuations because of AEs, there is a statistically significant difference to the disadvantage of neratinib compared with placebo. In both the intervention and the control arm, the median time to the event was not yet achieved.

Specific AEs

Specifically, for the specific adverse events, there are statistically significant differences to the disadvantage of neratinib compared with placebo with respect to gastrointestinal disorders (SOC, CTCAE grade ≥ 3), including diarrhoea (PT, CTCAE grade ≥ 3); fatigue (PT, CTCAE grade ≥ 3), metabolism and nutrition disorders, nervous system disorders, examinations (in each case SOC, CTCAE grade ≥ 3), skin and subcutaneous tissue disorders (SOC, AE), and muscle spasms (PT, AE).

Overall, the results on side effects show a moderate disadvantage for neratinib compared with the monitoring wait-and-see approach because of the increase in serious AEs as well as significant disadvantages because of an increase in severe AEs (CTCAE grade ≥ 3) and therapy discontinuations because of AEs; this results in a clear disadvantage overall. In detail, there are also exclusively negative effects in the area of specific AEs. Among the disadvantages in the side effects category, gastrointestinal disorders in particular (including diarrhoea) occurred.

Overall assessment

For the assessment of the additional benefit of neratinib for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago, results for the endpoint categories morbidity, quality of life, and side effects are available.

The assessment is based on the ExteNET study in which neratinib is compared with placebo. Based on the follow-up strategy implemented in the study, the comparison with placebo represents a suitable implementation of the appropriate comparator therapy, a “monitoring wait-and-see approach”. The results of the sub-population of patients with hormone receptor-positive breast cancer whose trastuzumab therapy has been completed for less than 1 year according to the approved therapeutic indication of neratinib are relevant for the assessment.

An evaluation of the overall survival endpoint was not planned for the data cut-off used, It is therefore not possible to assess the effects of extended adjuvant treatment with neratinib on overall survival based on the results available.

In the morbidity category, neratinib showed a clear, clinically relevant advantage compared with the monitoring wait-and-see approach in terms of in the study occurred disease relapses based on the endpoint relapse (operationalised as relapse rate and relapse-free survival). The prevention of relapses is an essential therapeutic goal in the present curative therapy situation.

In terms of health status (as measured by EQ-5D VAS) and health-related quality of life (measured by the FACT-B questionnaire), there are no statistically significant differences between treatment groups.

With regard to side effects, disadvantages are shown by an increase in the number of serious adverse events as well as clear disadvantages because of an increase in severe adverse events (CTCAE grade ≥ 3) and therapy discontinuations because of adverse events. In detail, there are also only disadvantages for the specific adverse events. Among the disadvantages in the side effects category, gastrointestinal disorders in particular (including diarrhoea) occurred.

In the overall view of the results for all available patient-relevant endpoints, a clear advantage with regard to the prevention of relapses is offset by clear disadvantages with regard to side effects. Data on overall survival are not available.

The disadvantages in the side effects category are weighted against the background of the curative therapy claim and do not completely question the advantages in preventing relapses.

As a result, for neratinib for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago, a minor additional benefit is determined.

Reliability of data (probability of additional benefit)

This assessment is based on the results of the randomised, double-blind, placebo-controlled ExteNET study in which neratinib is compared with placebo.

Because the benefit assessment is based on the results of only one study, at best indications of an additional benefit can be derived with regard to the reliability of data.

At the study level, the risk of bias is classified as low.

Against the background of the data cut-off used, the results on relapses are based on relatively small numbers of events and are therefore limited in their informative value.

Thus, the data basis shows uncertainties, which lead to a downgrading of the reliability of data for the overall assessment. Therefore, the reliability of data supporting the finding of an additional benefit must be classified as a “hint”.

2.1.4 Summary of the assessment

This assessment concerns the benefit assessment of the new medicinal product Nerlynx® with the active ingredient neratinib.

Neratinib is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

A monitoring wait-and-see approach was determined to be an appropriate comparator therapy by the G-BA.

For the assessment, the pharmaceutical company presents the results of the randomised, controlled, double-blind Phase III ExteNET study in which neratinib is compared with placebo. Based on the follow-up strategy implemented in the study, the comparison with placebo represents a suitable implementation of the appropriate comparator therapy, a “monitoring wait-and-see approach”. The results of the sub-population of patients with hormone receptor-positive breast cancer whose trastuzumab therapy has been completed for less than 1 year according to the approved therapeutic indication of neratinib from the first data cut-off of 7 July 2014 are relevant for the assessment.

Neratinib shows a clear, clinically relevant advantage in the prevention of relapses compared with a monitoring wait-and-see approach. The prevention of relapses is an essential therapeutic goal in the present curative therapy situation.

There are no data on overall survival. There are no statistically significant differences in health status and quality of life.

The advantage in terms of preventing relapses is offset by disadvantages because of an increase in the number of serious adverse events as well as significant disadvantages because of an increase in severe adverse events (CTCAE grade ≥ 3) and therapy discontinuations because of adverse events. The disadvantages are weighted against the background of the curative therapy claim.

Because of the low number of events, uncertainties remain with regard to the interpretation of the results of relapses.

In the overall view, there is a hint for a minor additional benefit of neratinib compared with the monitoring wait-and-see approach.

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 resolution will be based on the information from the dossier of the pharmaceutical company. However, it should be considered that the range of patient numbers presented is an underestimate. This is partly because the lower limit specified does not take into account prevalent adults. Furthermore, for neither the lower nor the upper limit are adults considered who have fallen ill in earlier years and who, for example as a result of a relapse, completed a (renewed) trastuzumab-based adjuvant therapy less than one year ago . On the other hand, only adults with breast cancer in Stages II and III are considered. Therefore, patients with stage I breast cancer are not represented. There is also an uncertainty for the proportion value of 10.1% for patients with hormone receptor- and HER2-positivity.

Overall, the patient numbers are subject to significant uncertainties. The number of patients in the SHI target population is closer to the upper limit than the lower limit.

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 Nerlynx® (active ingredient: neratinib) at the following publicly accessible link (last access: 30 April 2020):

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

Treatment with neratinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gynaecology and obstetrics, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with breast cancer.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on neratinib:

- Training material for doctors
- Informational material for patients

The training and information material include, in particular, Instructions on how to deal with the potential gastrointestinal toxicity (diarrhoea) associated with neratinib.

2.4 Treatment costs

The treatment costs are based on the statements of the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2020).

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

Treatment duration:

For the calculation of the annual therapy costs, the maximum therapy duration of one year (365 days) is assumed. The time unit “days” is used to calculate the “number of

treatments/patient/year", time between individual treatments, and for 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				
Neratinib	continuously for 1 year, 1x daily	365	1	365
Appropriate comparator therapy				
Monitoring wait-and-see approach	not quantifiable			

Usage and 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					
Neratinib	240 mg	240 mg	6 × 40 mg	365	2,190 × 40 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	not quantifiable				

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 Sections 130 and 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 product:

Designation of the therapy	Package 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					
Neratinib	180 FCT	€ 6,462.13	€ 1.77	€ 365.78	€ 6,094.58
Appropriate comparator therapy					
Monitoring wait-and-see approach	not quantifiable				
Abbreviations: FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 2020

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 assessed 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 standard expenditure in the course of the treatment are not shown.

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

3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 August 2019.

On 28 November 2019, the pharmaceutical company submitted a dossier for the benefit assessment of neratinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 November 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient neratinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 February 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 2 March 2020. The deadline for submitting written statements was 23 March 2020.

The oral hearing was held on 6 April 2020.

By letter dated 6 April 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 23 April 2020.

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 5 May 2020, and the proposed resolution was approved.

At its session on 14 May 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	27 August 2019	Determination of the appropriate comparator therapy
Working group Section 35a	1 April 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	6 April 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 April 2020 29 April 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	5 May 2020	Concluding discussion of the draft resolution
Plenum	14 May 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 14 May 2020

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

Prof. Hecken