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 Talazoparib (Breast Cancer, BRCA1/2-mutation, HER2-)

of 20 November 2020

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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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out based on 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 talazoparib 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 June 2020. 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 29 May 2020.

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 1 September 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 talazoparib 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 evaluated the data justifying the finding of an additional benefit based on their therapeutic relevance (qualitative) according to 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 set aside in the benefit assessment of talazoparib.

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 talazoparib (Talzenna) in accordance with the product information

Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced, or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germline; after prior therapy with an anthracycline and/or a taxane in the (neo)adjuvant or metastatic setting or not suitable for these treatments

Appropriate comparator therapy:

− Capecitabine

or

− Eribulin

or

− Vinorelbine

or

− An anthracycline- or taxane-containing therapy (only for patients who have not yet received anthracycline- and taxane-containing therapy or who are suitable for renewed anthracycline- or taxane-containing therapy)

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] 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.

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 applications 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. In terms of authorisation status, the active ingredients 5-fluorouracil, atezolizumab, bevacizumab, capecitabine, cyclophosphamide, docetaxel, doxorubicin, doxorubicin (liposomal), epirubicin, eribulin, gemcitabine, ifosfamide, methotrexate, mitomycin, mitoxantrone, olaparib, paclitaxel, nab-paclitaxel, vinblastine, vincristine, and vinorelbine are available for the treatment of HER2-negative locally advanced or metastatic breast cancer.

On 2. Non-medicinal treatment is not considered.

On 3 Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:
- Eribulin: Resolution of 22 January 2015
- Olaparib: Resolution of 16 January 2020
- Atezolizumab: Resolution of 2 April 2020

Guidelines:
Annex VI to Section K of the Pharmaceuticals Directive
Active ingredients that are not prescribable in off-label use:
- Gemcitabine in monotherapy for female breast cancer

Directive on methods of hospital treatment – Section 4 Methods excluded:
- Proton therapy for breast cancer

On 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines as well as systematic reviews of clinical studies.

In determining the appropriate comparator therapy, it was assumed that endocrine therapy alone is no longer indicated for the patients. Furthermore, it was assumed that the patients usually received taxane- and/or anthracycline-based chemotherapy as part of the previous chemotherapy.

According to the guidelines, further cytotoxic chemotherapy is recommended for patients with HER2-negative metastatic breast cancer who have undergone previous chemotherapeutic treatment for disease progression or relapse. With regard to cytotoxic chemotherapies, monotherapies should primarily be used. Only in cases of severe symptoms, rapid tumour growth, and aggressive tumour behaviour is polychemotherapy indicated.

Because of the high value of anthracyclines and taxanes in the treatment of breast cancer, they can be considered for patients who have not yet received anthracycline- and/or taxane-containing therapy or as re-therapy if individual requirements are met.

Of those primarily recommended in guidelines, in addition to taxanes and anthracyclines, capecitabine, vinorelbine, and eribulin are approved for use as monotherapy in the intended therapeutic indication.

For eribulin used to treat patients who have experienced further progression after at least one chemotherapy for advanced breast cancer, the G-BA has found a hint for a

considerable additional benefit compared with capecitabine or vinorelbine monotherapy for patients who can no longer be treated with taxanes or anthracyclines (resolution of 22 January 2015). Because of the low reliability of data and the restriction of the additional benefit to part of the approved therapeutic indication, eribulin is considered an equally appropriate therapeutic option alongside capecitabine and vinorelbine.

In the benefit assessment on olaparib, with the resolution of 16 January 2020, a minor additional benefit For the treatment of adult patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germline previously treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting or who were ineligible for these treatments, a hint for a minor additional benefit was established. For atezolizumab in combination with nab-paclitaxel for the treatment of locally advanced or metastatic triple-negative breast cancer (PD-L1 expression ≥ 1%), there was a hint for a non-quantifiable additional benefit compared with systemic therapy containing anthracycline and/or taxane (resolution of 2 April 2020). Because olaparib and atezolizumab are still quite new treatment options and their therapeutic value cannot yet be conclusively assessed, they are currently not considered as appropriate comparator therapies.

In summary, “capecitabine or vinorelbine or eribulin or possibly an anthracycline- or taxane-containing therapy” was therefore determined as the appropriate comparator therapy for talazoparib as monotherapy in the present therapeutic indication.

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 talazoparib is assessed as follows:

For the treatment of adult patients and patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germline; after prior therapy with an anthracycline and/or a taxane in the (neo)adjuvant or metastatic setting or ineligible for these treatments, there is a hint for a considerable additional benefit.

Justification:

To demonstrate the additional benefit of talazoparib for the treatment of locally advanced or metastasised breast cancer, the pharmaceutical company has presented the results of the EMBRACA study.

EMBRACA is a multi-centric, open, randomised controlled study comparing talazoparib with chemotherapy according to the doctor’s instructions using capecitabine or vinorelbine or eribulin or gemcitabine. The ongoing global study, which started in October 2014, included adult patients with HER2-negative, locally advanced or metastatic breast cancer with BRCA1/2 mutations in the germline. Patients had to have been pre-treated with an anthracycline and taxane in the (neo-)adjuvant or metastatic situation except in the presence of a contraindication. Hormone receptor-positive patients also had to have received at least one endocrine therapy in the adjuvant or metastatic situation and underwent disease progression, or they had to have been ineligible for endocrine therapy. For the locally advanced or metastatic stage of the disease, a maximum of three previous chemotherapy lines were allowed.

The 431 patients included were randomised 2:1 in the talazoparib arm (N = 287) and in the arm with chemotherapy according to the doctor’s instructions (N = 144). The individual therapy was selected before randomisation. Gemcitabine, does not represent a therapeutic option in accordance with the appropriate comparative therapy defined by the G-BA. For this reason, the pharmaceutical company presents evaluations of the modified intention-to-treat (mITT) population from which patients from both treatment arms randomised to gemcitabine were

excluded. The exclusion results in 266 patients in the talazoparib arm and 130 patients in the chemotherapy arm.

The EMBRACA is conducted in 145 study centres in Asia, Australia, Europe, and North and South America.

For the present benefit assessment, the 2nd data cut-off of 30 September 2019 is used.

Extent and probability of the additional benefit

Mortality

In the EMBRACA study, overall survival was defined as the time between randomisation and death regardless of the underlying cause of death.

For the endpoint overall survival, there was no statistically significant difference between the treatment groups. As a result, no additional benefit is identified for the overall survival endpoint.

Morbidity

Progression-free survival (PFS)

In the EMBRACA study, progression-free survival was the primary endpoint and was defined as the time between randomisation and disease progression (determined by a central, independent, and blinded radiological committee (IRF) using RECIST criteria Version 1.1) or death by any cause.

For progression-free survival, there was a statistically significant difference between the treatment groups in favour of talazoparib.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was surveyed as an independent endpoint using the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology

In the EMBRACA study, symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the additional breast cancer specific module EORTC QLQ-BR23.

The survey was conducted during treatment on the first day of each treatment cycle and at the final round.

In addition to evaluations of the time to first clinically relevant deterioration, the pharmaceutical company also presented evaluations of the time to permanent deterioration of the symptomatology.

Even at the start of study, the proportion of completed questionnaires was lower in the chemotherapy arm than in the talazoparib arm. As the study progresses, the return rate decreases more in the chemotherapy arm than in the talazoparib arm because of the earlier progression. From the responder analyses presented, the evaluation of the time to first clinically relevant deterioration (increase of the score by at least 10 points compared with baseline) is used.

For the endpoints fatigue, pain, insomnia, loss of appetite, side effects of systemic therapy, and symptoms chest and arm areas, there was a statistically significant difference in favour of talazoparib compared with chemotherapy. For the endpoint “burden of hair loss”, there were no usable data. For all further endpoints, there was no statistically significant difference between the study arms.

In the overall view, the results on symptomatology show positive effects of talazoparib treatment on several symptoms of both the cancer- and breast cancer-specific symptomatology surveyed. These are assessed as a considerable improvement in symptoms compared with treatment with capecitabine, vinorelbine, or eribulin.

Quality of life

In the EMBRACA study, the functional scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module EORTC QLQ-BR23 were used to assess the health-related quality of life.

The survey was conducted during treatment on the first day of each treatment cycle and at the final round.

In addition to evaluations of the time to first clinically relevant deterioration, the pharmaceutical company also presented evaluations of the time to permanent deterioration of the symptomatology.

Even at the start of study, the proportion of completed questionnaires was lower in the chemotherapy arm than in the talazoparib arm. As the study progresses, the return rate decreases more in the chemotherapy arm than in the talazoparib arm because of the earlier progression. Therefore, from the responder analyses presented, the evaluation of the time to first clinically relevant deterioration (decrease of the score by at least 10 points compared with baseline) is used.

For all items of the EORTC QLQ-C30 (i.e. global health status as well as the functional scales physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning, and body image of the EORTC QLQ-BR23), there was a statistically significant difference to the advantage of talazoparib. For the endpoint “sexual enjoyment”, there were no usable data. There was no statistically significant difference between the study arms for the endpoints sexual functioning and future perspectives.

In view of the positive effects on several or on the majority of the endpoints on cancer- and breast cancer-specific health-related quality of life surveyed, some of which are also significant, there is an advantage of talazoparib treatment compared with treatment with capecitabine, vinorelbine, or eribulin in terms of health-related quality of life, the extent of which can be assessed as a significant improvement overall.

Side effects

Total adverse events (AE)

All endpoints in the side effects category were collected up to 30 days after the last dose of the study medication.

In the EMBRACA study, 98.5% of the patients in the intervention arm and 97.4% in the comparator arm experienced an adverse event.

Serious adverse events (SAE)

For the serious adverse events, there was no statistically significant difference between the study arms.

Severe AE (CTCAE grade 3 or 4)

A statistically significant difference to the advantage of talazoparib was found with regard to severe adverse events with CTCAE grade 3 or 4.

Discontinuation because of AE

For the endpoint “therapy discontinuation because of AE”, there was no statistically significant difference between the study arms.

Specific AE

Specific AE were selected by the IQWiG using events based on frequency and differences between treatment arms and taking into account patient relevance.

There were statistically significant advantages for talazoparib in terms of the specific AE eye disorders, hand-foot syndrome, and paraesthesia as well as the specific severe AE (CTCAE grade ≥ 3) skin and subcutaneous tissue disorders, neutropoenia, and diarrhoea. In contrast, for talazoparib, there were statistically significant disadvantages in terms of the specific severe AE (CTCAE grade ≥ 3) anaemia and thrombocytopenia. In the overall consideration of the endpoints on specific AE, the positive effects of talazoparib predominate.

In the side effects category, an overall advantage of talazoparib compared with capecitabine, vinorelbine, or eribulin can thus be observed.

Overall assessment/conclusion

For the assessment of the additional benefit of talazoparib, results from the open, randomised, controlled EMBRACA study in comparison to capecitabine, vinorelbine, or eribulin on mortality (overall survival), morbidity, quality of life and side effects are available.

In the endpoint category mortality, the results available for the overall survival endpoint do not show a statistically significant effect in relation to the total population of the study. No additional benefit is identified for the overall survival endpoint.

The results on symptomatology show positive effects of talazoparib treatment on several symptoms of both the cancer- and breast cancer-specific symptomatology surveyed. These are assessed as a considerable improvement in symptoms compared with treatment with capecitabine, vinorelbine, or eribulin.

In view of the positive effects on several or on the overwhelming majority of the endpoints on cancer- and breast cancer-specific health-related quality of life surveyed, some of which are also significant, there is an advantage of talazoparib treatment, the extent of which can be assessed as a significant improvement overall.

In terms of side effects, talazoparib has an advantage over capecitabine, vinorelbine, or eribulin in terms of the endpoint severe adverse events (CTCAE grade 3 or 4). No difference were found for the endpoints serious AE and discontinuation because of AE. There are both advantages and disadvantages for the specific AE; however, the positive effects outweigh them. In the side effects category, an overall advantage of talazoparib compared with capecitabine, vinorelbine, or eribulin can thus be observed.

Based on the clear advantages in the endpoint categories of morbidity (symptomatology) and health-related quality of life, which are also particularly relevant in this advanced therapy situation, and based on the advantages in the side effects category, the G-BA found a considerable additional benefit for talazoparib compared with capecitabine, vinorelbine, or eribulin.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open-label, randomised controlled EMBRACA study.

The risk of bias at the study level is classified as high. At the endpoint level, the risk of bias for all endpoints is estimated to be high. In particular, the patient-reported endpoints on symptomatology and health-related quality of life, which were surveyed using the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires, are considered to be potentially highly biased because of the open study design and thus the lack of blinding. In the EMBRACA study a high proportion of patients in the chemotherapy arm withdrew their consent after randomisation and consequently did not receive any study medication. This also contributes to the uncertainty.

For these reasons, the reliability of data for the additional benefit determined is considered as a hint.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Talzenna with the active ingredient talazoparib. Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced, or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.

The appropriate comparator therapy was determined by the G-BA as follows:

- Capecitabine *or*
- Eribulin *or*
- Vinorelbine *or*
- An anthracycline- or taxane-containing therapy (only for patients who have not yet received anthracycline- and taxane-containing therapy or who are suitable for renewed anthracycline- or taxane-containing therapy)

For the assessment of the additional benefit of talazoparib, results from the open, randomised, controlled EMBRACA study in comparison to capecitabine, vinorelbine, or eribulin on mortality (overall survival), morbidity, quality of life and side effects are available.

In the endpoint category mortality, for the endpoint overall survival, there was no statistically significant difference between treatment groups.

The results on morbidity (symptomatology) and health-related quality of life show positive effects of treatment with talazoparib. These are assessed as a significant improvement overall.

In terms of side effects, talazoparib has an advantage in terms of severe adverse events (CTCAE grade 3 or 4). No difference was found for serious AE and discontinuation because of AE. With respect to specific AE, the positive effects of talazoparib predominate. In the side effects category, an overall advantage of talazoparib can be derived.

Because of the open study design and the high proportion of withdrawn consent forms in the chemotherapy arm, there is expected to be a high risk of bias in the morbidity, quality of life, and side effects categories. With regard to the reliability of data, therefore, only a hint for an additional benefit can be derived.

In the overall view, there is a hint for a considerable additional benefit of talazoparib compared with capecitabine, vinorelbine, or eribulin.

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 information from the dossier of the pharmaceutical company. This information is subject to uncertainties. This is due to methodological weaknesses, insufficient data basis, and under- and overestimates. Uncertainties arise in particular because of the lack of consideration of longer observation periods for prevalence estimation, patients with transition to advanced stages, and patients for whom an anthracycline and/or a taxane was not suitable.

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 Talzenna (active ingredient: talazoparib) at the following publicly accessible link (last access: 27 August 2020):

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

Treatment with talazoparib 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 locally advanced or metastatic breast cancer.

The selection of patients for breast cancer treatment with Talzenna should be based on the detection of a pathogenic or suspected pathogenic *BRCA* germline mutation using a validated test procedure by an experienced laboratory.

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 November 2020).

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

For doxorubicin and epirubicin, the cumulative total dose was considered (450–550 mg/m² for doxorubicin and 900–1,000 mg/m² for epirubicin, respectively). For doxorubicin and epirubicin there is product information with different dosage recommendations (doxorubicin: 50–80 mg/m² and 60–75 mg/m²; epirubicin: 75–90 mg/m² and 60–90 mg/m². The dosage recommendations with the largest range were used for the cost calculation: doxorubicin 50–80 mg/m² and epirubicin: 60–90 mg/m². The "Consumption" table shows only those dosage regimens that, when calculated, give the range of annual treatment costs.

For dosages depending on body surface area (BSA), the average body measurements of adult females were used as a basis (average height: 1.66 m, average body weight: 68.7 kg). From this, a body surface area of 1.76 m² is calculated (calculation according to Du Bois 1916)[2]

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Talazoparib	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Capecitabine	2 × daily on day 1–14 of a 21-day cycle	17.4	14	243.6

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Vinorelbine	1 × per week	52	1	52
Eribulin	On Day 1 and 8 of a 21-day cycle	17.4	2	34.8
An anthracycline- or taxane-containing therapy				
Docetaxel	1 × every 21 days	17.4	1	17.4
Doxorubicin	1 × every 21 days	5–11[3]	1	5–11
Doxorubicin, pegylated	1 × every 28 days	13	1	13
Epirubicin	1 × every 21 days	10–16[4]	1	10–16
Paclitaxel	1 × every 21 days	17.4	1	17.4
nab-paclitaxel	1 × every 21 days	17.4	1	17.4

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					
Talazoparib	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg
Appropriate comparator therapy					
Capecitabine	2,150 mg[5]	4,300 mg	8 × 500 mg + 2 × 150 mg	243.6	1,948.8 × 500 mg + 487.2 × 150 mg
Vinorelbine	25 mg/m² = 44 mg – 30 mg/m² = 52.8 mg	44 mg – 52.8 mg	1 × 50 mg – 1 × 50 mg + 1 × 10 mg	52	52 × 50 mg – 52 × 50 mg + 52 × 10 mg
Eribulin	1.23 mg/m² = 2.16 mg	2.16 mg	3 × 0.88 mg	34.8	104.4 × 0.88 mg
Anthracycline- or taxane-containing therapy					

[3] Based on the total cumulative dose of maximum 450–550 mg/m².
[4] Based on the total cumulative dose of maximum 900–1,000 mg/m².
[5] Product information for capecitabine (Xeloda®): Standard dose for BSA 1.67–1.78: 2,150 mg.

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Docetaxel	100 mg/m² = 176 mg	176 mg	1 × 160 mg + 1 × 20 mg	17.4	17.4 × 160 mg + 17.4 × 20 mg
Doxorubicin	80 mg/m² = 140.8 mg – 50 mg/m² = 88 mg	140.8 mg - 88 mg	1 × 150 mg 1 × 100 mg	5 – 11	5 × 150 mg 11 × 100 mg
Pegylated liposomal doxorubicin (PLD)	50 mg/m² = 88 mg	88 mg	2 × 20 mg + 1 × 50 mg	13	26 × 20 mg + 13 × 50 mg
Epirubicin	90 mg/m² = 158.4 mg – 90 mg/m² = 158.4 mg	158.4 mg 158.4 mg	1 × 100 mg + 1 × 50 mg + 1 × 10 mg 1 × 100 mg + 1 × 50 mg + 1 × 10 mg	10 – 11	10 × 100 mg + 10 × 50 mg + 10 × 10 mg 11 × 100 mg + 11 × 50 mg + 11 × 10 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 × 300 mg + 1 × 30 mg	17.4	17.4 × 300 mg + 17.4 × 30 mg
nab-paclitaxel	260 mg/m² = 457.6 mg	457.6 mg	5 × 100 mg	17.4	87 × 100 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 Sections 130 and 130 a 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					
Talazoparib	30 HC	€ 7,025.08	€ 1.77	€ 408.30	€ 6,615.01
Appropriate comparator therapy					
Capecitabine 500 mg[6]	120 FCT	€ 147.75	€ 1.77	€ 11.12	€ 134.86
Capecitabine 150 mg[6]	120 FCT	€ 52.51	€ 1.77	€ 3.39	€ 47.35
Docetaxel 160 mg	1 CIS	€ 1,362.13	€ 1.77	€ 175.44	€ 1,184.92
Docetaxel 20 mg	1 CIS	€ 168.06	€ 1.77	€ 7.66	€ 158.63
Doxorubicin 100 mg[6]	1 CIS	€ 278.32	€ 1.77	€ 0.00	276.55
Doxorubicin 150 mg[6]	1 SFI	€ 407.54	€ 1.77	€ 0.00	405.77
Pegylated liposomal doxorubicin (PLD) 20 mg	1 CIS	€ 753.11	€ 1.77	€ 42.16	€ 709.18
Pegylated liposomal doxorubicin (PLD) 50 mg	1 CIS	€ 1,855.15	€ 1.77	€ 105.41	€ 1,747.97
Eribulin 0.88 mg	6 SFI	€ 2,368.44	€ 1.77	€ 135.48	€ 2,231.19
Epirubicin 100 mg	1 CIS	€ 292.99	€ 1.77	€ 13.74	€ 277.48
Epirubicin 50 mg	1 CIS	€ 151.26	€ 1.77	€ 6.84	€ 142.65
Epirubicin 10 mg	1 CIS	€ 38.25	€ 1.77	€ 1.34	€ 35.14
Paclitaxel 300 mg	1 CIS	€ 872.24	€ 1.77	€ 41.94	€ 828.53
Paclitaxel 30 mg	1 CIS	€ 112.60	€ 1.77	€ 4.96	€ 105.87
nab-paclitaxel 100 mg	1 PIS	€ 418.27	€ 1.77	€ 52.91	€ 363.59
Vinorelbine 50 mg	10 CIS	€ 1,388.38	€ 1.77	€ 67.07	€ 1,319.54
Vinorelbine 10 mg	10 CIS	€ 286.33	€ 1.77	€ 13.42	€ 271.14
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIS = powder for the preparation of an infusion solution					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 November 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

[6] Fixed reimbursement rate

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.

Cost per package	Costs after deduction of statutory rebates[7]	Cost per service[8,9]	Treatment days per year	Costs per patient per year
Paclitaxel				
Pre-medication: Dexamethasone 2 × 20 mg/day, oral				
50 × 20 mg: € 115.62 (FB)	€ 113.85 (€ 1.77; €0.00)	€ 4.55	17.4	€ 79.24
Antihistamine: Dimetindene 1 mg per 10 kg BW, i.v. [10]				
5 × 4 mg: € 18.15	€ 14.46 (€ 1.77; € 1.92)	€ 5.78	17.4	€ 100.64
Ranitidine: 50 mg/day, i.v.				
5 × 50 mg: € 14.70	€ 12.74 (€1.77; € 0.19)	€ 2.55	17.4	€ 44.34

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*; contract on price formation for substances and preparations of substances; Sections 4 and 5 Pharmaceutical Price Ordinance) of 1 October 2009 is not fully used to calculate the 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 *Hilfstaxe* in its currently valid version, surcharges for the production of parenteral preparations containing cytostatic agents of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the *Hilfstaxe*. The cost representation is based on the pharmacy sales 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 according to the regulations in Annex 3 of the *Hilfstaxe*.

7 Section 130 SGB V and Section 130a SGB V
8 Proportionate costs of costs per package for consumption per treatment day
9 Rounded interim result
10 For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were used as the basis (average height: 1.66 m, average body weight: 68.7 kg). Source: German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

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

At its session on 29 January 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. At its session on 28 May 2019, the Subcommittee on Medicinal Products redefined the appropriate comparator therapy.

On 29 May 2020, the pharmaceutical company submitted a dossier for the benefit assessment of talazoparib 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 May 2020 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 talazoparib.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 August 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 September 2020. The deadline for submitting written statements was 22 September 2020.

The oral hearing was held on 6 October 2020.

By letter dated 6 October 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 30 October 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 10 November 2020, and the proposed resolution was approved.

At its session on 20 November 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	29 January 2019	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	28 May 2019	Redefinition of the appropriate comparator therapy
Working group Section 35a	29 September 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	6 October 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 October 2020 3 November 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	10 November 2020	Concluding discussion of the draft resolution
Plenum	20 November 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 November 2020

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

Prof. Hecken