# Resolution

Gemeinsamer Bundesausschuss

## 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

At its session on 20 November 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

**I. Annex XII shall be amended in alphabetical order to include the active ingredient talazoparib as follows:**

**Talazoparib**

Resolution of: 20 November 2020
Entry into force on: 20 November 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

**Therapeutic indication (according to the marketing authorisation of 20 June 2019):**

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 (see Section 5.1). 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.

## 1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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)

**Extent and probability of the additional benefit of talazoparib compared with capecitabine or vinorelbine or eribulin:**

Hint for a considerable additional benefit

**Study results according to endpoints:[1]**

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

EMBRACA study: Talazoparib vs chemotherapy according to the doctor's instructions (capecitabine or vinorelbine or eribulin or gemcitabine)

[1] Data from the dossier assessment of the IQWiG (A20-48) and the addendum (A20-89) unless otherwise indicated.

Study design: RCT, open, parallel

Relevant sub-population: Talazoparib vs chemotherapy according to the doctor's instructions with the use of capecitabine or vinorelbine or eribulin

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ Risk of bias | Summary |
|---|---|---|
| Mortality | ↔ | No difference relevant for the benefit assessment. |
| Morbidity | ↑ | Advantages in pain, insomnia, loss of appetite, and chest symptoms |
| Health-related quality of life | ↑ | Advantages in health status, physical, social, and emotional functioning, role functioning, and body image |
| Side effects | ↑ | Advantage in the endpoint severe AE (CTCAE grade 3 or 4) |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |

**Mortality**

| Endpoint | Talazoparib | | Chemotherapy according to the doctor's instructions [a] | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI] *Patients with event n (%)* | N | Median time to event in months [95% CI] *Patients with event n (%)* | HR [95% CI] p value |
| **Mortality** | | | | | |
| Overall survival | 266 | 19.6 [16.7; 22.7] *199 (74.8)* | 130 | 19.8 [17.6; 22.4] *97 (74.6)* | 0.86 [0.67; 1.10]; 0.236 |

**Morbidity**

| Endpoint | Talazoparib | | Chemotherapy according to the doctor's instructions [a] | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI] *Patients with event n (%)* | N | Median time to event in months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| **Progression-free survival (PFS) [b]** | | | | | |
| | 266 | 8.5 [7.1; 9.2] *173 (65)* | 130 | 5.6 [3.3; 8.2] *74 (56.9)* | 0.541 [0.41; 0.72]; < 0.0001 2.9 months |
| **Symptomatology** | | | | | |
| *EORTC QLQ-C30 symptom scales – time to first deterioration[c]* | | | | | |
| Fatigue | 243 | 2.1 [1.5; 2.8] *166 (68.3)* | 104 | 1.5 [1.4; 1.9] *69 (66.3)* | 0.74 [0.55; 0.99]; 0.043 0.6 months |
| Nausea and vomiting | 243 | 3.8 [2.3; 7.5] *139 (57.2)* | 104 | 3.0 [1.5; 11.3] *51 (49.0)* | 0.93 [0.66; 1.30]; 0.659 |
| Pain | 243 | 5.7 [4.0; 9.7] *130 (53.5)* | 104 | 2.9 [1.6; 4.9] *61 (58.7)* | 0.55 [0.40; 0.75]; < 0.001 2.8 months |
| Dyspnoea | 243 | 8.4 [5.6; 10.8] *122 (50.2)* | 104 | 7.8 [5.1; n.c.] *36 (34.6)* | 0.99 [0.67; 1.45]; 0.94 |
| Insomnia | 243 | 10.4 [7.0; 17.1] *109 (44.9)* | 104 | 3.2 [1.8; 8.1] *53 (51.0)* | 0.54 [0.38; 0.76]; < 0.001 7.2 months |
| Loss of appetite | 243 | 7.4 [4.9; 11.9] *128 (52.7)* | 104 | 2.3 [1.5; 4.2] *58 (55.8)* | 0.60 [0.44; 0.84]; 0.002 5.1 months |
| Constipation | 243 | 7.2 [5.7; 10.1] *118 (48.6)* | 104 | 10.1 [3.7; n.c.] *37 (35.6)* | 1.03 [0.70; 1.50]; 0.884 |
| Diarrhoea | 243 | 10.7 [8.2; 16.0] *103 (42.4)* | 104 | n.a. [3.5; n.c.] *34 (32.7)* | 0.79 [0.53; 1.19]; 0.256 |

| Endpoint | Talazoparib | | Chemotherapy according to the doctor's instructions [a] | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI] *Patients with event n (%)* | N | Median time to event in months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| *EORTC QLQ-BR23 symptom scales – time to first deterioration*[c] | | | | | |
| Side effects of the systemic therapy | 243 | 9.3 [5.8; 12.5] *119 (49.0)* | 104 | 3.5 [2.1; 10.6] *50 (48.1)* | 0.65 [0.46; 0.92]; 0.013 5.8 months |
| Symptoms in the chest area | 243 | 37.4 [23.5; n.c.] *59 (24.3)* | 104 | 12.5 [8.8; n.c.] *29 (27.9)* | 0.54 [0.34; 0.86]; 0.008 24.9 months |
| Symptoms in the arm area | 243 | 6.9 [4.2; 14.9] *122 (50.2)* | 104 | 3.9 [2.1; 11.9] *49 (47.1)* | 0.70 [0.50; 0.99]; 0.044 3 months |
| Burden of hair loss | No usable data | | | | |

**Health-related quality of life**

| Endpoint | Talazoparib | | Chemotherapy according to the doctor's instructions [a] | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI] *Patients with event n (%)* | N | Median time to event in months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| *EORTC QLQ-C30 functional scales – time to first deterioration*[d] | | | | | |
| Global health status | 243 | 5.7 [3.8; 7.8] *130 (53.5)* | 104 | 3.3 [2.1; 5.0] *55 (52.9)* | 0.61 [0.44; 0.85]; 0.003 2.4 months |
| Physical functioning | 243 | 9.3 [7.7; 14.9] *109 (44.9)* | 104 | 2.8 [2.1; 6.6] *53 (51.0)* | 0.51 [0.36; 0.72]; < 0.001 6.5 months |
| Role functioning | 243 | 4.6 [3.5; 6.6] *135 (55.6)* | 104 | 1.7 [1.1; 3.0] *64 (61.5)* | 0.56 [0.41; 0.77]; < 0.001 2.9 months |
| Cognitive functioning | 243 | 4.4 [3.0; 7.5] *141 (58.0)* | 104 | 2.8 [1.7; 3.7] *56 (53.8)* | 0.71 [0.51; 0.98]; 0.038 1.6 months |

| Endpoint | Talazoparib | | Chemotherapy according to the doctor's instructions [a] | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI] *Patients with event n (%)* | N | Median time to event in months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| Emotional functioning | 243 | 10.7 [6.4; 24.3] *101 (41.6)* | 104 | 3.5 [2.3; 9.9] *49 (47.1)* | 0.54 [0.38; 0.77]; < 0.001 7.2 months |
| Social functioning | 243 | 8.2 [4.9; 12.5] *122 (50.2)* | 104 | 2.3 [1.6; 4.9] *54 (51.9)* | 0.60 [0.43; 0.84]; 0.003 5.9 months |
| *EORTC QLQ-BR23 functional scales – time to first deterioration*[d] | | | | | |
| Body image | 243 | 17.7 [11.5; n.c.] *88 (36.2)* | 104 | 4.9 [2.8; n.c.] *42 (40.4)* | 0.56 [0.38; 0.81]; 0.002 12.8 months |
| Sexual functioning | 243 | 32.8 [7.5; n.c.] *92 (37.9)* | 104 | 14.0 [3.6; n.c.] *33 (31.7)* | 0.95 [0.63; 1.42]; 0.799 |
| Sexual enjoyment | No usable data | | | | |
| Future perspective | 243 | n.a. [24.8; n.c.] *68 (28.0)* | 104 | n.a. [6.1; n.c.] *27 (26.0)* | 0.70 [0.44; 1.11]; 0.129 |

**Side effects**

| Endpoint | Talazoparib | | Chemotherapy according to the doctor's instructions [a] | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI] *Patients with event n (%)* | N | Median time to event in months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| **Adverse events** (presented additionally) | | | | | |
| | 265 | 0.2 [0.1; 0.3] *261 (98.5)* | 114 | 0.1 [0.1; 0.2] *111 (97.4)* | – |
| **Serious adverse events (SAE)** | | | | | |
| | 265 | 20.7 [15.3; 31.1] *95 (35.8)* | 114 | n.a. [6.7; n.c.] *33 (28.9)* | 0.75 [0.49; 1.13]; 0.162 |

| Endpoint | Talazoparib | | Chemotherapy according to the doctor's instructions [a] | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI] *Patients with event n (%)* | N | Median time to event in months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| **Severe adverse events (CTCAE grade 3 or 4)** | | | | | |
| | 265 | 3.5 [2.8; 4.0] *183 (69.1)* | 114 | 2.0 [1.3; 3.5] *72 (63.2)* | 0.73 [0.55; 0.97]; 0.027 1.5 months |
| **Therapy discontinuation because of adverse events** | | | | | |
| | 265 | n.a. *21 (7.9)* | 114 | n.a. *10 (8.8)* | 0.59 [0.27; 1.27]; 0.169 |
| **Specific adverse events** | | | | | |
| Myelodysplastic syndrome[e] (PT, CTCAE-grade ≥ 3) | 265 | *0 (0)* | 114 | *0 (0)* | n.c. |
| Acute myeloid leukaemia[f] (PT, CTCAE grade ≥ 3) | 265 | *0 (0)* | 114 | *0 (0)* | n.c. |
| Hand-foot syndrome (PT, AEs)[g] | 265 | n.a. *4 (1.5)* | 114 | n.a. *28 (24.6)* | 0.05 [0.02; 0.14]; < 0.001 |
| Anaemia (PT, CTCAE grade ≥ 3) | 265 | 18.1 [11.6; n.c.] *103 (38.9)* | 114 | n.a. *5 (4.4)* | 7.23 [2.93; 17.79]; < 0.001 |
| Thrombocytopenia (PT, CTCAE grade ≥ 3) | 265 | n.a. *22 (8.3)* | 114 | n.a. *1 (0.9)* | 8.34 [1.12; 61.98]; 0.013 |
| Neutropoenia (PT, CTCAE grade ≥ 3) | 265 | n.a. *50 (18.9)* | 114 | n.a. *26 (22.8)* | 0.61 [0.38; 0.99]; 0.044 |
| Diarrhoea (PT, CTCAE grade ≥ 3) | 265 | n.a. *2 (0.8)* | 114 | n.a. [11.8; n.c.] *6 (5.3)* | 0.12 [0.02; 0.58]; 0.002 |
| Skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3) | 265 | n.a. *2 (0.8)* | 114 | n.a. [16,5; n.c.] *8 (7.0)* | 0.04 [0.01; 0.32]; < 0.001 |

| Endpoint | Talazoparib | | Chemotherapy according to the doctor's instructions [a] | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI] *Patients with event n (%)* | N | Median time to event in months [95% CI] *Patients with event n (%)* | HR [95% CI] p value Absolute difference (AD)[a] |
| Eye disorders (SOC, AEs) | 265 | n.a. *35 (13.2)* | 114 | 20.0 [20.0; n.c.] *21 (18.4)* | 0.38 [0.21; 0.68]; < 0.001 |
| Paresthesia (PT, AEs) | 265 | n.a. *13 (4.9)* | 114 | n.a. *14 (12.3)* | 0.23 [0.10; 0.53]; < 0.001 |

a Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
b Data from dossier on talazoparib Module 4A from 21 February 2019, data cut-off of 15 September 2017.
c An increase of the respective score by at least 10 points was regarded as a clinically relevant deterioration.
d A decrease of the respective score by at least 10 points was regarded as a clinically relevant deterioration.
e For MDS, the pharmaceutical company considers the SMQ MDS, which is not a sufficiently specific operationalisation for the present benefit assessment. The SMQ MDS results show that 1 (0.4%) patient in the talazoparib arm and no patient in the chemotherapy arm experienced a severe event (CTCAE grade ≥ 3).
f The pharmaceutical company states that the SMQ AML is to be considered although it is not an SMQ according to MedDRA but rather a compilation of PTs predefined by the pharmaceutical company, which does not represent a sufficiently specific operationalisation for the present benefit assessment. In the compilation of PTs to AML considered by the pharmaceutical company, no patient in the talazoparib arm and one (0.9%) patient in the chemotherapy arm experienced a severe event (CTCAE grade ≥ 3).
g 1 (0.4 %) patient in the talazoparib arm and 3 (2.6%) patients in the chemotherapy arm had a severe hand-foot syndrome (CTCAE grade ≥ 3).

Abbreviations used:
AD = absolute difference; AML = acute myeloid leukaemia; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organization for Research and Treatment of Cancer; HR = hazard ratio; CI = confidence interval; MDS = myelodysplastic syndrome; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with (at least one) event; N= number of patients evaluated; n.c = not calculable; n.a. = not achieved; PT = preferred term; QLQ-BR23 = Quality of Life Questionnaire – Breast Cancer 23; QLQ-C30 = Quality of Life Questionnaire Cancer-30; SMQ = standardised MedDRA query; SOC = system organ class; SAE = serious adverse event; AE = adverse event

## 2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 410–1,830 patients

## 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.

## 4. Treatment costs

**Annual treatment costs:**

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

| Designation of the therapy | Annual treatment costs/patient |
|---|---|
| Medicinal product to be assessed: | |
| Talazoparib | € 80,482.62 |
| Appropriate comparator therapy: | |
| Capecitabine | € 2,382.37 |
| Vinorelbine | € 6,861.61 – 8,271.54 |
| Eribulin | € 38,822.71 |
| Anthracycline- or taxane-containing therapy | |
| Docetaxel | € 23,377.77 |
| Doxorubicin | € 2,028.85 – 3,042.05 |
| Pegylated liposomal doxorubicin (PLD) | € 41,162.29 |
| Epirubicin | € 4,552.70 – 5,007.97 |
| Paclitaxel<br>Additionally required SHI services<br>Total: | € 16,258.56<br>€ 224.22<br>€ 16,482.78 |
| nab-paclitaxel | € 31,632.33 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 November 2020

Other services covered by SHI funds:

| Designation of the therapy | Type of service | Costs/ unit | Number/ cycle | Number/ patient/ year | Costs/ patient/ year |
|---|---|---|---|---|---|
| Vinorelbine | Surcharge for production of a parenteral preparation containing cytostatic agents | € 81 | 1 | 52 | € 4,212 |

| | | | | | |
|---|---|---|---|---|---|
| Eribulin | Surcharge for production of a parenteral preparation containing cytostatic agents | € 81 | 2 | 34.8 | € 2,818.80 |
| Docetaxel | Surcharge for production of a parenteral preparation containing cytostatic agents | € 81 | 1 | 17.4 | €1,409.40 |
| Doxorubicin | Surcharge for production of a parenteral preparation containing cytostatic agents | € 81 | 1 | 5–11 | € 405 – 891 |
| Pegylated liposomal doxorubicin (PLD) | Surcharge for production of a parenteral preparation containing cytostatic agents | € 81 | 1 | 13 | € 1,053 |
| Epirubicin | Surcharge for production of a parenteral preparation containing cytostatic agents | € 81 | 1 | 10–16 | € 810 – 1,296 |
| Paclitaxel | Surcharge for production of a parenteral preparation containing cytostatic agents | € 81 | 1 | 17.4 | €1,409.40 |
| nab-paclitaxel | Surcharge for production of a parenteral preparation containing cytostatic agents | € 81 | 1 | 17.4 | €1,409.40 |

**II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 20 November 2020.**

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 20 November 2020

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

Prof. Hecken