# Summary of Product Characteristics

## 1. Name of the Medicinal Product

TALZENNA 0.25 mg hard capsules

TALZENNA 1 mg hard capsules

## 2. Qualitative and Quantitative Composition

TALZENNA 0.25 mg hard capsules

Each capsule contains 0.363 mg talazoparib tosylate equivalent to 0.25 mg talazoparib free base.

TALZENNA 1 mg hard capsules

Each capsule contains 1.453 mg talazoparib tosylate equivalent to 1 mg talazoparib free base.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule.

TALZENNA 0.25 mg hard capsules

Opaque, size #4 hard hypromellose (HPMC) capsule with an ivory cap (printed with “Pfizer” inblack) and a white body (printed with “TLZ 0.25” in black).

TALZENNA 1 mg hard capsules

Opaque, size #4 hard hypromellose (HPMC) capsule with a light red cap (printed with “Pfizer”in black) and a white body (printed with “TLZ 1” in black).

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

TALZENNA is indicated for the treatment of adult patients with germline breast cancer susceptibility gene (BRCA)-mutated human epidermal growth factor receptor 2 (HER2)-negativelocally advanced or metastatic breast cancer.

### 4.2 Posology and method of administration

Treatment with TALZENNA should be initiated and supervised by a physician experienced inthe use of anticancer medicinal products.

Detection of mutations in hereditary breast cancer-related BRCA1 and BRCA2 genes should bedetermined by an experienced laboratory using a validated test method (see Section 5.1).

Posology

The recommended dose of TALZENNA is 1 mg capsule taken orally once daily. Patients shouldbe treated until disease progression or unacceptable toxicity occurs.

*Missing dose*

If the patient vomits or misses a dose, an additional dose should not be taken.
The nextprescribed dose should be taken at the usual time.

*Dose modifications*

To manage adverse reactions, consider interruption of treatment or dose reduction based on severity and clinical presentation. Recommended dose reductions are indicated in Table 1.

**Table 1. Dose Modification for Toxicities**

| | **Dose Level** |
|---|---|
| Recommended starting dose | 1 mg (one 1 mg capsule) once daily |
| First dose reduction | 0.75 mg (three 0.25 mg capsules) once daily |
| Second dose reduction | 0.5 mg (two 0.25 mg capsules) once daily |
| Third dose reduction | 0.25 mg (one 0.25 mg capsule) once daily |

Complete blood count should be obtained prior to starting TALZENNA therapy and monitoredmonthly and as clinically indicated (see Table 2 and Section 4.4).

**Table 2. Dose Modification and Management**

| | **Withhold TALZENNA until levels resolve to** | **Resume TALZENNA** |
|---|---|---|
| Haemoglobin <8 g/dL | ≥9 g/dL | Resume TALZENNA at areduced dose |
| Platelet count <50,000/μL | ≥50,000/μL | |
| Neutrophil count <1,000/μL | ≥1,500/μL | |
| Non-haematologic adverse reaction Grade 3 or Grade 4 | Grade 1 | Consider resuming TALZENNA at a reduced dose or discontinue |

*Concomitant treatment with inhibitors of P-glycoprotein (P-gp)*

Strong inhibitors of P-gp may lead to increased talazoparib exposure. Concomitant use of strong P-gp inhibitors during treatment with talazoparib should be avoided. Co administration shouldonly be considered after careful evaluation of the potential benefits and risks. If coadministration with a strong P-gp inhibitor is unavoidable, the TALZENNA dose should be reduced to the next lower dose. When the strong P-gp inhibitor is discontinued, the TALZENNA dose should be increased (after 3–5 half-lives of the P-gp inhibitor) to the dose used prior to the initiation of the strong P-gp inhibitor (see Section 4.5).

*Concomitant treatment with inhibitors of Breast Cancer Resistance Protein (BCRP)*

The effect of coadministration of BCRP inhibitors with TALZENNA has not been studied. Therefore, concomitant use of strong BCRP inhibitors during treatment with talazoparib shouldbe avoided (see Section 4.5).

Special populations

*Hepatic impairment*

No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤1 × upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST). TALZENNA has not been studied in

patients with moderate (total bilirubin >1.5 to 3.0 × ULN and any AST) or severe hepatic impairment (totalbilirubin >3.0 × ULN and any AST) (see Section 5.2).

*Renal impairment*

No dose adjustment is required for patients with mild renal impairment (60 mL/min ≤ creatinine clearance [CrCL] <90 mL/min). For patients with moderate renal impairment (30 mL/min ≤ CrCL
<60 mL/min), the recommended dose of TALZENNA is 0.75 mg once daily. For patients with severe renal impairment (15 mL/min ≤ CrCL < 30 mL/min), the recommended dose of TALZENNA is 0.5 mg once daily. TALZENNA has not been studied in patients requiring hemodialysis (see Section 5.2).

*Elderly population*

No dose adjustment is necessary in elderly (≥65 years of age) patients (see Section 5.2).

*Pediatric population*

The safety and efficacy of TALZENNA in children and adolescents <18 years of age have notbeen established.

**4.3 Contraindications**

None.

**4.4 Special warnings and precautions for use**

Myelosuppression

Myelosuppression consisting of anemia, leukopenia/neutropenia, and/or thrombocytopenia, havebeen reported in patients treated with talazoparib (see Section 4.8). Do not start talazoparib untilpatients have recovered from hematological toxicity caused by previous therapy (≤ Grade 1).

Precautions should be taken to routinely monitor hematology parameters and signs and symptoms associated with anemia, leukopenia/neutropenia, and/or thrombocytopenia in patients receiving talazoparib. If such events occur, dose modifications (reduction or interruption) are recommended (see Section 4.2).

Supportive care with or without blood and/or platelet transfusions and/or administration of colony stimulating factors may be used as appropriate.

Myelodysplastic syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML) have been reported in patients who received poly(adenosine diphosphate [ADP] ribose) polymerase (PARP) inhibitors. In the Phase 3 randomized breast cancer study, MDS/AML was reported in no patients who received talazoparib and in 1 out of 126 (0.8%) patients who received chemotherapy. Overall, MDS/AML has been reported in 1 out of 561 (0.2%) solid tumor patients treated with talazoparib in clinical studies. Potential contributing factors for the development of MDS/AML include previous platinum-containing chemotherapy, other DNA damaging agents or radiotherapy.

Complete blood counts should be obtained at baseline and monitored monthly for signs of hematologic toxicity during treatment. If MDS/AML is confirmed, talazoparib should be discontinued.

Embryo-fetal toxicity

Studies in animals have shown embryo-fetal toxicity and talazoparib was clastogenic in in vitro and in in vivo assays (see Section 5.3). Talazoparib should not be given to pregnant patients or those who plan to become pregnant during treatment. Women of childbearing potential should be advised to avoid becoming pregnant while receiving TALZENNA. TALZENNA may cause fetal harm when administered to a pregnant woman. Advice pregnant women of the potential risk to the fetus (see Section 4.6).

A highly effective method of contraception is required for female patients during treatment with TALZENNA, and for at least 7 months after completing therapy. Advise male patients with female partners of reproductive potential and pregnant partners to use effective contraception (even after vasectomy), during treatment with TALZENNA and for at least 4 months after the final dose.

**4.5 Interaction with other medicinal products and other forms of interaction**

Talazoparib is a substrate for drug transporters P-gp and BCRP and mainly eliminated by renal clearance as unchanged compound.

Agents that may affect talazoparib plasma concentrations

*Effect of P-gp inhibitors*

Data from a drug-drug interaction study in patients with advanced solid tumors indicated that coadministration of multiple daily doses of a P-gp inhibitor, itraconazole 100 mg twice daily with a single 0.5 mg talazoparib dose increased talazoparib total exposure ($AUC_{inf}$) and peak concentration ($C_{max}$) by approximately 56% and 40%, respectively, relative to a single 0.5 mg talazoparib dose administered alone. Population pharmacokinetic (PK) analysis has shown that concomitant use of strong P-gp inhibitors with TALZENNA increased talazoparib exposure by 44.7%, relative to TALZENNA given alone. If patients must be coadministered a strong P-gp inhibitor, those that result in ≥2-fold increase in the exposure of an in vivo probe P-gp substrate, (including but not limited to amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valspodar, andverapamil), reduce the TALZENNA dose to 0.75 mg once daily (see Section 4.2).

Population PK analysis has shown that coadministration with relatively weak P-gp inhibitors (including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin) in clinical studies had no significant effect on talazoparib exposure.

*Effect of P-gp inducers*

Data from a drug-drug interaction study in patients with advanced solid tumors indicated that coadministration of a P-gp inducer (rifampin 600 mg once daily) with a single 1 mg talazoparib dose increased talazoparib $C_{max}$ by 37% with no effect on talazoparib exposure.

*Effect of BCRP inhibitors*

The effect of BCRP inhibitors on PK of talazoparib has not been studied. Concomitant use of strong BCRP inhibitors (including but not limited to curcumin, cyclosporine, and elacridar [GF120918]) should be avoided (see Section 4.2).

*Effect of acid-reducing agents*

Population PK analysis indicates that coadministration of acid-reducing agents including proton pump inhibitors (PPI), histamine receptor 2 antagonists ($H_2$RA), or other acid-reducing agents had no significant impact on the absorption of talazoparib.

**4.6 Fertility, pregnancy and lactation**

Women of childbearing potential/contraception in males and females

Women of childbearing potential should not become pregnant while receiving TALZENNA andshould not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of child bearing potential prior to treatment (see Section 4.4).

A highly effective method of contraception is required for female patients during treatment with TALZENNA, and for at least 7 months after completing therapy. Advise male patients with female partners of reproductive potential and pregnant partners to use a condom (even after vasectomy) during treatment with TALZENNA and for at least 4 months after the final dose (seeSection 4.4).

Pregnancy

There are no data from the use of TALZENNA in pregnant women. Studies in animals have shown embryo-fetal toxicity (see Section 5.3). TALZENNA may cause fetal harm when administered to a pregnant woman. TALZENNA is not recommended during pregnancy or forwomen of childbearing potential not using contraception (see Section 4.4).

Breastfeeding

It is unknown whether TALZENNA is excreted in human breast milk. A risk to newborns/infants cannot be excluded and therefore breastfeeding is not recommended duringtreatment with TALZENNA and for at least 1 month after the final dose.

Fertility

There is no information on fertility in patients. Based on non-clinical findings in testes andovary, male and female fertility may be compromised by treatment with

TALZENNA (seeSection 5.3).

**4.7 Effects on ability to drive and use machines**

No studies have been conducted on the effects of talazoparib on the ability to drive or operate machinery. However, patients experiencing fatigue/asthenia or dizziness while taking talazoparibshould exercise caution when driving or operating machinery.

**4.8 Undesirable effects**

The overall safety profile of TALZENNA is based on pooled data from 494 patients who received talazoparib at 1 mg daily in clinical studies for solid tumors, including 286 patients from a randomized Phase 3 study with germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer and 83 patients from a nonrandomized Phase 2 study in patients with germline BRCA-mutated locally advanced or metastatic breast cancer.

The most common (≥25%) adverse reactions in patients receiving talazoparib in these clinical studies were fatigue (57.1%), anaemia (49.6%), nausea (44.3%), neutropenia (30.2%), thrombocytopenia (29.6%), and headache (26.5%). The most common (≥10%) Grade ≥3 adversereactions of talazoparib were anaemia (35.2%), neutropenia (17.4%), and thrombocytopenia (16.8%).

Dose modifications (dose reductions or dose interruptions) due to any adverse reaction occurred in 62.3% of patients receiving TALZENNA. The most common adverse reactions leading to dose modifications were anaemia (33.0%), neutropenia (15.8%), and thrombocytopenia (13.4%).

Permanent discontinuation due to an adverse reaction occurred in 3.6% of patients receiving TALZENNA. The median duration of exposure was 5.4 months (range 0.03-61.1).

**Table 3: Adverse Reaction Table***

| System Organ Class | Adverse Reactions |
|---|---|
| Blood and lymphatic system disorders | Anaemia[a]<br>Neutropenia[b]<br>Thrombocytopenia[c]<br>Leukopenia[d]<br>Lymphopenia[e] |
| Metabolism and nutrition disorders | Decreased appetite |
| Nervous system disorders | Headache<br>Dizziness<br>Dysgeusia |
| Gastrointestinal disorders | Nausea<br>Vomiting<br>Diarrhoea<br>Abdominal pain[f]<br>Dyspepsia<br>Stomatitis |
| Skin and subcutaneous tissue disorders | Alopecia |
| General disorders and administrationsite conditions | Fatigue[g] |

* There were no Grade 5 adverse reactions.

a. Includes preferred terms of anaemia, haematocrit decreased, and haemoglobin decreased.

b. Includes preferred terms of neutropenia and neutrophil count decreased

c. Includes preferred terms of thrombocytopenia and platelet count decreased.

d. Includes preferred terms of leukopenia and white blood cell count decreased.

e. Includes preferred terms of lymphocyte count decreased and lymphopenia.

f. Includes preferred terms of abdominal pain, abdominal pain upper, abdominal discomfort, and abdominalpain lower.

g. Includes preferred terms of fatigue and asthenia.

**Reporting of suspected adverse reactions:**

Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local country requirements.

### 4.9 Overdose

There is no specific treatment in the event of talazoparib overdose, and symptoms of overdose are not established. In the event of overdose, treatment with talazoparib should be stopped, and physicians should consider gastric decontamination, follow general supportive measures and treat symptomatically.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Mechanism of action and pharmacodynamic effects

TALZENNA is a potent inhibitor of PARP enzymes, PARP1, and PARP2. PARP enzymes are involved in cellular DNA damage response signaling pathways such as DNA repair, gene transcription, cell cycle regulation, and cell death. PARP inhibitors (PARPi) exert cytotoxic effects on cancer cells by 2 mechanisms, inhibition of PARP catalytic activity and by PARP trapping, whereby PARP protein bound to a PARPi does not readily dissociate from a DNA lesion, thus preventing DNA repair, replication, and transcription and ultimately leading to apoptosis and/or cell death. Treatment of cancer cell lines that are harboring defects in DNA repair genes with talazoparib single agent leads to increased γH2AX level, which is a marker of double stranded DNA breaks, resulting in decreased cell proliferation and increased apoptosis. The potent cytotoxicity observed with talazoparib against multiple tumor cell lines harboring mutations in the DNA damage response (DDR) pathways, can be attributed to its inhibition of PARP catalytic activity and robust PARP trapping. Talazoparib anti-tumor activity was also observed in the patient-derived xenograft (PDX) BRCA-mutant breast cancer model that was previously treated with a platinum-based regimen. In the PDX model talazoparib decreased tumor growth and increased γH2AX level and apoptosis in the tumors.

*Detection of BRCA mutation*

Patients are eligible for TALZENNA treatment if they have a confirmed deleterious or suspected deleterious germline BRCA mutation (i.e., a mutation that disrupts normal gene function; detectedusing an appropriately validated test).

Clinical efficacy and safety

*Randomized Phase 3 study EMBRACA*

EMBRACA was an open-label, randomized, parallel, 2-arm multicenter study of TALZENNA versus chemotherapy (capecitabine, eribulin, gemcitabine, vinorelbine) in patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer who received no more than 3 prior cytotoxic chemotherapy regimens for their metastatic or locally advanced disease. Patients were required to have received treatment with an anthracycline and/or a taxane (unless contraindicated) in the neoadjuvant, adjuvant and/or metastatic setting. Patients with prior platinum therapy for advanced disease were required to have no evidence of disease progression during platinum therapy. No prior treatment with a PARP inhibitor was permitted.

A total of 431 patients were randomized 2:1 to receive TALZENNA 1 mg capsules once daily or chemotherapy at standard doses until progression or unacceptable toxicity. Of the 431 patients randomized onto EMBRACA, 287 were randomized to the TALZENNA arm and 144 to the chemotherapy arm. Randomization was stratified by prior use of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status (triple-negative breast cancer [TNBC] versus non-TNBC), and history of central nervous system metastasis (yes versus no).

The majority of patients 408/431 (95%) were selected using the BRAC*Analysis* test and BRCA mutation status (breast cancer susceptibility gene 1 [BRCA1] positive or breast cancer susceptibility gene 2 [BRCA2] positive) was similar across both treatment arms.

Patient demographic and baseline characteristics were generally similar between the study treatment arms. The median age of patients treated with TALZENNA was 45 years (range 27 to 84) and 50 years (range 24 to 88) among patients treated with chemotherapy. Of note, 63% versus 47% of patients were <50 years of age in the

talazoparib and chemotherapy arms, respectively, 27% versus 47% were 50 to <65 years of age, and 9% versus 7% were ≥65 years of age. Among all randomized patients, 1% versus 2% were males, 66.9% versus 75.0% were White; 10.8% versus 11.1% were Asian, and 4.2% versus 0.7% were Black or African American in the talazoparib and chemotherapy arms, respectively. Almost all patients (97.7%) in both arms had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Approximately 55.9% of patients had hormone receptor-positive (either estrogen receptor [ER]-positive- or progesterone receptor [PR]-positive) disease; 44.1% of patients had
triple-negative disease and the proportions were balanced across treatment arms. The median time from initial diagnosis of breast cancer to diagnosis of advanced breast cancer was 1.9 years (range 0 to 22) on the talazoparib arm and 2.7 years (range 0 to 24) on the chemotherapy arm. The reported disease-free interval (DFI) was <12 months in 37.6% of patients on the talazoparib arm and in 29.2% of patients on the chemotherapy arms. Among all patients enrolled, the median number of prior cytotoxic regimens for advanced breast cancer was 1 where 38.3% of patients received no prior regimens for advanced or metastatic disease, 37.4% received 1, 19.7% received 2, and 4.6% received >3 prior regimens, respectively. Sixteen percent of patients in the talazoparib arm and 20.8% of patients in the chemotherapy arm had received prior platinum treatment.

The primary efficacy endpoint was progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by blinded independent central review (BICR). The secondary objectives were objective response rate (ORR), overall survival (OS), safety, and PK. Exploratory objectives included duration of response (DOR), Clinical Benefit Rate at 24 weeks (CBR24), quality of life (QoL) assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30)/EORTC Quality of Life Questionnaire – Breast Cancer Module (QLQ-BR23) and biomarker research.

The study met its primary objective of demonstrating a statistically significant

improvement in PFS for TALZENNA compared with chemotherapy (hazard ratio [HR] 0.54; 95% confidence interval [CI]: 0.41, 0.71; p-value <0.0001). A sensitivity analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results. The OS interim analysis was performed at 51% for the total number of planned events. Efficacy data for EMBRACA are summarized in Table 4 and the Kaplan-Meier curves for PFS and OS are shown in Figures 1 and 3. Consistent results were observed across pre-specified patient subgroups (Figure 2).

**Table 4. Summary of Efficacy Results – EMBRACA Study**

| | **Talazoparib** | **Chemotherapy** |
|---|---|---|
| Progression-Free Survival by BICR | N=287 | N=144 |
| Events, number (%) | 186 (65%) | 83 (58%) |
| Median (95% CI), months | 8.6 (7.2, 9.3) | 5.6 (4.2, 6.7) |
| Hazard ratio (95% CI) | 0.54 (0.41, 0.71) | |
| 2-sided p-value[a] | p<0.0001 | |
| Overall Survival (interim analysis)[b] | N=287 | N=144 |
| Events, number (%) | 108 (38%) | 55 (38%) |
| Median (95% CI), months | 22.3 (18.1, 26.2) | 19.5 (16.3, 22.4) |
| Hazard ratio (95% CI) | 0.76 (0.55, 1.06) | |
| 2-sided p-value[a] | p=0.1053 | |
| Objective Response by Investigator[c,d] | N=219 | N=114 |
| ORR (%, 95% CI) | 62.6 (55.8, 69.0) | 27.2 (19.3, 36.3) |
| Odds ratio (95% CI) | 4.99 (2.9, 8.8) | |
| 2-sided p-value[e] | p<0.0001 | |
| Duration of Response by Investigator[c] | N=137 | N=31 |
| Median (IQR), months | 5.4 ( 2.8, 11.2) | 3.1 (2.4, 6.7) |

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CMH=Cochran-Mantel- Haenszel; CR=complete response; IQR=interquartile range; ITT=intent-to-treat; ORR=objective

response rate;

OS=overall survival; PR=partial response; RECIST 1.1=response Evaluation Criteria in Solid Tumorsversion 1.1; SD=stable disease.

[a.] Stratified Log-rank test.

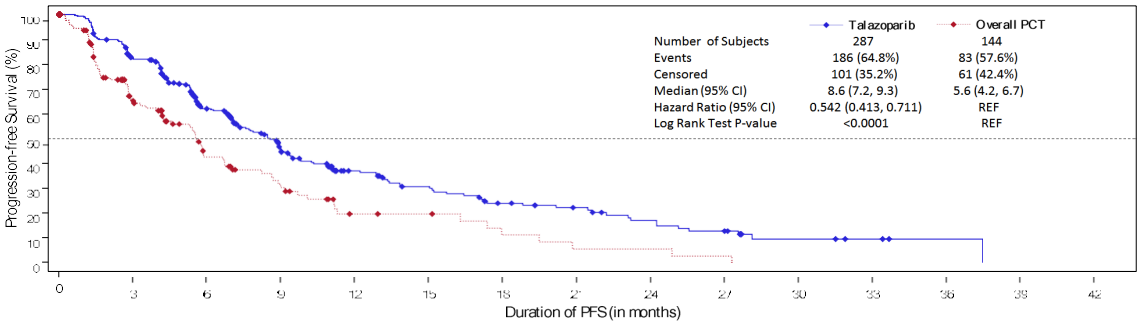
[b.] 51% of the projected final number of OS events occurred (163 of 321 deaths).

[c.] Conducted in ITT with measurable disease population who had an objective response. The complete responserate was 5.5% for talazoparib compared to 0% for the chemotherapy arm.

[d.] Per RECIST 1.1, confirmation of CR/PR was not required.

[e.] Stratified CMH test.

## Figure 1. Kaplan-Meier Curves of PFS – EMBRACA Study



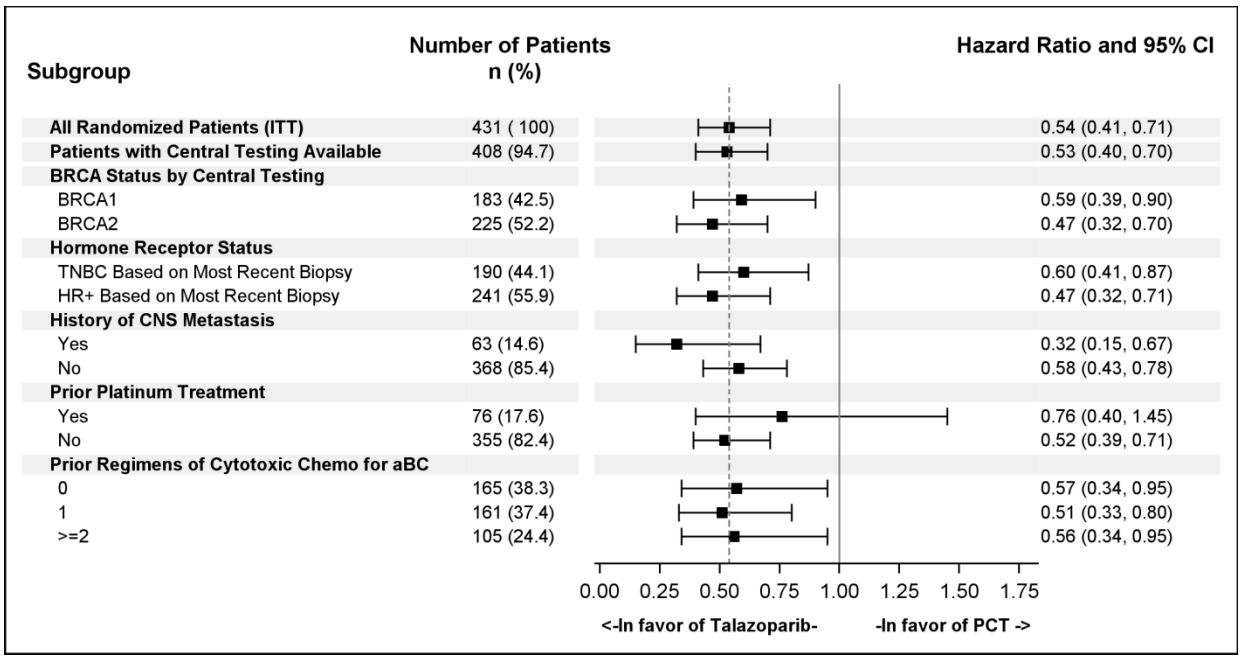

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Talazoparib: Evt/Cum. | 0/0 | 50/50 | 53/103 | 34/137 | 17/154 | 9/163 | 9/172 | 2/174 | 5/179 | 4/183 | 2/185 | 0/185 | 0/185 | 1/186 | 0/186 |
| Patients at Risk | 287 | 229 | 148 | 91 | 55 | 42 | 29 | 23 | 16 | 12 | 5 | 3 | 1 | 0 | 0 |
| Overall PCT: Evt/Cum. | 0/0 | 41/41 | 20/61 | 8/69 | 7/76 | 0/76 | 3/79 | 2/81 | 0/81 | 1/82 | 1/83 | 0/83 | 0/83 | 0/83 | 0/83 |
| Patients at Risk | 144 | 68 | 34 | 22 | 9 | 8 | 4 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 |

Primary analysis p-value was based on a stratified log-rank test. Hazard ratio was based on stratified Cox regression model with treatment as the only covariate (stratification factors: number of prior cytotoxic chemotherapy regimens, triple-negative status, history of central nervous system metastasis) and was relative to overall chemotherapy with

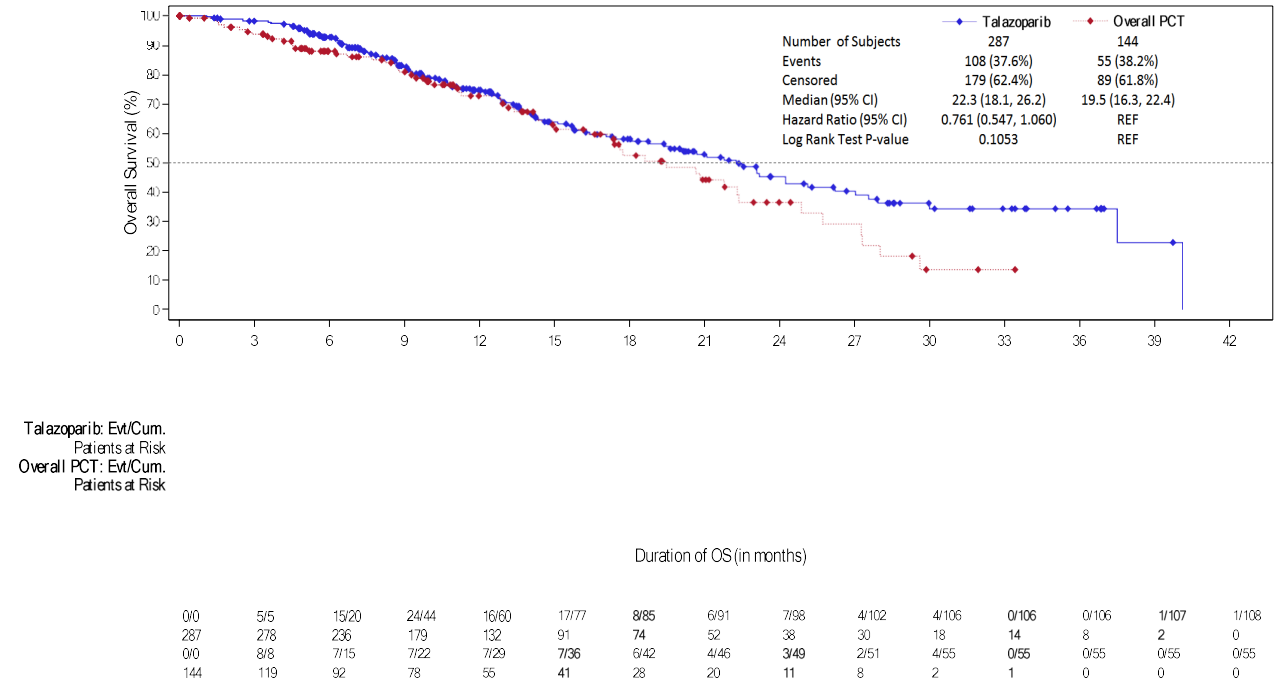
<1 favoring talazoparib.

Abbreviations: CI=confidence interval; cum=cumulative; Evt=event; PFS=progression-free survival; PCT=physician's choice treatment (chemotherapy); REF=reference treatment group.

## Figure 2. Forest Plot for PFS Analyses for Key Subgroups – EMBRACA Study




## Figure 3. Kaplan-Meier Curves of Overall Survival – EMBRACA Study



Abbreviations: CI=confidence interval; Cum.=cumulative; Evt=event; OS=overall survival; PCT=physician's choicetreatment (chemotherapy); REF=reference treatment group.

Patient-reported symptoms were assessed using the EORTC QLQ-C30 and its EORTC QLQ-BR23. A total of 262 patients in the talazoparib arm and 114 patients in the chemotherapyarm completed the questionnaire at baseline and at least 1 postbaseline visit.

A significantly greater overall improvement from baseline in global health status (GHS)/QoL was observed in the talazoparib arm (3.0 [95% CI: 1.2, 4.8]) compared to the chemotherapy arm (-5.4 [95% CI: -8.8, -2.0]) ($p<0.0001$). A significantly greater delay in time to clinically meaningful (≥10 point decrease from baseline) definitive deterioration in GHS/QoL was observed in the talazoparib arm compared with chemotherapy [(HR: 0.38 [95% CI: 0.26, 0.55]; $p<0.0001$), median 24.3 months versus 6.3 months].

A significantly greater overall improvement from baseline in breast symptoms was observed in the talazoparib arm (-5.1 [95% CI: -6.7, -3.5]) compared to the chemotherapy arm (-0.1 [95% CI:
-2.9, 2.6]) ($p=0.002$). A significantly greater delay in time to clinically meaningful (≥10 pointincrease from baseline) definitive deterioration in breast symptoms was observed in the talazoparib arm compared with chemotherapy (HR of 0.39 [95% CI: 0.20, 0.78]; $p=0.005$, median times not reached [NR]).

A significantly greater overall improvement from baseline was observed in the talazoparib arm compared to the chemotherapy arm in role functioning [12.4, 95% CI: (7.1, 17.7) ($p<0.0001$)] and the following symptoms: fatigue [-12.3, 95% CI: (-17.2, -7.5) ($p<0.0001$)], pain [-13.3, 95%
CI: (-18.5, -8.1) ($p<0.0001$)] and appetite loss [-11.7, 95% CI: (-17.6, -5.7) ($p=0.0001$)].

A significantly greater delay in time to clinically meaningful deterioration in the following symptoms was observed in the talazoparib arm compared to the chemotherapy arm for fatigue, [(HR: 0.40 [95% CI: 0.28, 0.56]; $p<0.0001$), median 17.1 months versus 7.1 months], pain,

[(HR: 0.34 [95% CI: 0.23, 0.50]; p<0.0001), median 22.7 months versus 7.5 months], appetite
loss, [(HR: 0.32 [95% CI: 0.21, 0.49]; p<0.0001), median NR versus 9.0 months], systemic
therapy side effects, [(HR: 0.33 [95% CI: 0.22, 0.51]; p<0.0001), median 24.6 months versus
7.9 months], arm symptoms, [(HR: 0.46 [95% CI: 0.29, 0.73]; p=0.0008), median NR versus
13.2 months]. A significantly greater delay in time to clinically meaningful deterioration was observed in the talazoparib arm compared to the chemotherapy arm for role functioning, [(HR: 0.36 [95% CI: 0.25, 0.52]; p<0.0001), median 20.5 months versus 5.6 months].

**5.2 Pharmacokinetic properties**

Talazoparib exposure generally increased proportionally with dose across the range of 0.025 mg to 2 mg after daily administration of multiple doses. Following repeated daily dosing of 1 mg talazoparib to patients, the geometric mean area under the plasma concentration-time curve (AUC) and maximum observed plasma concentration ($C_{max}$) of talazoparib at steady-state was in the range of 126 ng•hr/mL to 208 ng•hr/mL and 11.4 ng/mL to 19.1 ng/mL, respectively.

Following repeated daily dosing, talazoparib plasma concentrations reached steady-state within 2 to 3 weeks. The median accumulation ratio of talazoparib following repeated oral administration of 1 mg once daily was in the range of 2.33 to 5.15.

Absorption

Following oral administration of talazoparib, the median time to $C_{max}$ ($T_{max}$) was generally between 1 to 2 hours after dosing. The absolute bioavailability study has not been conducted in humans. However, based on urinary excretion data the absolute bioavailability is at least 54.6% with fraction absorbed of at least 68.7% (see Elimination).

*The effect of food*

Food intake decreased the rate but not the extent of talazoparib absorption. Following a

single oral dose of talazoparib with high-fat, high-calorie food (approximately 827 calories, 57% fat), the mean $C_{max}$ of talazoparib was decreased by approximately 46%, the median $T_{max}$ was delayed from 1 to 4 hours, while the $AUC_{inf}$ was not affected. Based on these results, TALZENNA can be administered with or without food.

Distribution

The population means apparent volume of distribution ($V_{ss}/F$) of talazoparib was 420 L. In vitro, talazoparib is approximately 74% bound to plasma proteins with no concentration dependence over the concentration range of 0.01 µM to 1 µM. Renal impairment does not appear to impact talazoparib protein binding as there was no obvious trend in the mean talazoparib fraction of unbound drug ($f_u$) in human plasma in vivo with worsening renal function.

Metabolism

Talazoparib undergoes minimal hepatic metabolism in humans. Following oral administration of a single 1 mg dose of [C]talazoparib to humans, no major circulating metabolites were identified in plasma, and talazoparib was the only circulating drug-derived entity identified. No metabolites that individually represented more than 10% of the administered dose were recovered in the urine or feces. The identified metabolic pathways of talazoparib in humans include:

1) mono-oxidation; 2) dehydrogenation; 3) cysteine conjugation of mono-desfluoro-talazoparib; and 4) glucuronide conjugation.

In vitro, talazoparib was not an inhibitor of cytochrome (CYP)1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 or inducer of CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

In vitro, talazoparib did not inhibit any of the major intestinal, hepatic or renal membrane transporters (P-gp, BCRP, organic anion transporting polypeptide [OATP]1B1, OATP1B3, organic cationic transporter [OCT]1 OCT2, organic anion transporter [OAT]1, OAT3, bile saltexport pump [BSEP], multidrug and toxin extrusion [MATE]1 and MATE2-K) at clinically relevant concentrations.

In vitro, talazoparib did not inhibit any of the major uridine-diphosphate glucuronosyltransferase (UGT) isoforms (1A1, 1A4, 1A6, 1A9, 2B7, and 2B15) at clinically relevant concentrations.

Elimination

The mean terminal plasma half-life of talazoparib was 89.8 hours and the population mean apparent oral clearance (CL/F) was 6.45 L/h in cancer patients. In 6 female patients with advanced solid tumors given a single oral dose of [C]talazoparib, a mean of 68.7% and 19.7% of the total administered radioactive dose was recovered in urine and feces, respectively. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 54.6% of the administered dose, while unchanged talazoparib recovered in the feces accounted for 13.6%.

Age, sex, race, and body weight

A population PK analysis was conducted using data from 490 patients with cancer to evaluate the impact of age (ranging from 18 to 88 years), sex (53 males and 437 females), race (361 White, 41 Asian, 16 Black, 9 Others, and 63 Not reported), and body weight (ranging from 35.7 kg to 162 kg) on the PK of talazoparib. The results have shown that age, sex, race, and bodyweight had no clinically relevant effect on the PK of talazoparib.

Pediatric population

Pharmacokinetics of talazoparib have not been evaluated in patients <18 years of age.

Elderly population

Of the 494 patients who received TALZENNA, 85 patients were ≥65 years of age. No overall differences in safety or effectiveness of TALZENNA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

Renal impairment

Data from a PK trial in advanced cancer patients with varying degrees of renal impairment indicate that talazoparib total exposure ($AUC_{0-24}$) after multiple

talazoparib once-daily dosesincreased by 12%, 43%, and 163% in patients with mild (eGFR 60 - 89 mL/min/1.73 $m^2$), moderate (eGFR 30 - 59 mL/min/1.73 $m^2$), and severe (eGFR 15 - 29 mL/min/1.73 $m^2$) renal impairment, respectively, relative to patients with normal renal function
(eGFR ≥90mL/min/1.73 $m^2$). Talazoparib $C_{max}$ increased by 11%, 32%, and 89% in patients with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function. Consistent with these findings, a population PK analysis that included 490 patients, where 132 patients had mild renal impairment (60 mL/min ≤CrCL <90 mL/min), 33 patients had moderate renal impairment (30 mL/min ≤ CrCL <60 mL/min), and 1 patient had severe renal impairment (CrCL <30 mL/min), showed that talazoparib CL/F was decreased by 14.4% and 37.1% in patients with mild and moderate renal impairment, corresponding to 17% and 59% increase in AUC, respectively, when compared to patients with normal renal function
(CrCL ≥90 mL/min). The PK of talazoparib has not been studied in patients requiringhemodialysis.

Hepatic impairment

Based on a population PK analysis that included 490 patients, where 118 patients had mild hepatic impairment (total bilirubin ≤1.0 × ULN and AST > ULN, or total bilirubin >1.0 to
1.5 × ULN and any AST), mild hepatic impairment had no effect on the PK of talazoparib. The PK of talazoparib have not been studied in patients with moderate (total bilirubin >1.5 to
3.0 × ULN and any AST) or severe hepatic impairment (total bilirubin >3.0 × ULN and anyAST).

Cardiac electrophysiology

The effect of talazoparib on cardiac repolarization was evaluated using time-matched electrocardiograms (ECGs) in assessing the relationship between the change of the QT interval corrected for heart rate (QTc) from baseline and the corresponding plasma talazoparib concentrations in 37 patients with advanced solid tumors. Talazoparib did not have a clinically relevant effect on QTc prolongation at the maximum clinically recommended dose of 1 mg oncedaily.

**5.3 Preclinical safety data**

Carcinogenicity

Carcinogenicity studies have not been conducted with talazoparib.

Genotoxicity

Talazoparib was not mutagenic in a bacterial reverse mutation (Ames) test. Talazoparib was clastogenic in an in vitro chromosomal aberration assay in human peripheral blood lymphocytesand in an in vivo micronucleus assay in rats at exposures similar to clinically relevant doses. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of talazoparib, indicating the potential for genotoxicity in humans.

Repeat-dose toxicity

In repeat-dose toxicity studies of up to 13-week duration, talazoparib was clinically tolerated in rats at 0.04 mg/kg/day and in dogs at 0.01 mg/kg/day and the $AUC_{24}$ exposure margins at the no adverse effect level are 0.2-fold the relevant human exposure. The main findings at subtherapeutic exposures included bone marrow hypocellularity with dose-dependent decrease in hematopoietic cells, depletion of lymphoid tissue in multiple organs and atrophy and/or degenerative changes in testes, epididymis, and seminiferous tubules. Additional findings at higher exposures included dose-dependent increase in apoptosis/necrosis in the gastrointestinal (GI) tract, liver, and ovary.

Most of the histopathologic findings were generally reversible while the testes findings were partially reversible after 4 weeks of dosing cessation. These toxicity findings are consistent withthe pharmacology of talazoparib and its tissue distribution pattern.

Reproductive toxicology

In an embryo-fetal development study in rats, talazoparib resulted in embryo-fetal death, fetal malformation (depressed eye bulge, small eye, split sternebra, fused cervical vertebral arch) and structural variations in bones at a maternal systemic $AUC_{24}$ exposure approximately 0.09-fold the relevant human exposure at the recommended dose.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Talazoparib capsules content

Silicified microcrystalline cellulose (sMCC)

Capsule shell

*White body shell* Hypromellose (HPMC)

Titanium dioxide (E171)

**Ivory cap**

Hypromellose (HPMC), Yellow iron Oxide (E172)and Titanium dioxide (E171)

**Light red cap**

Hypromellose (HPMC), Red iron oxide (E172), Yellow iron oxide (E172) and Titanium dioxide (E171)

Printing ink

Shellac Propylene glycol, Ammonium hydroxide, Black iron oxide and Potassium hydroxide

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

Do not use TALZENNA after the expiry date which is stated on the Carton/Bottle labelafter .

### 6.4 Special precautions for storage

Store below 30 °C

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

TALZENNA 0.25 mg hard capsules

High-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat induction seal (HIS) liner, containing 30 or 60 or 90 hard capsules.

TALZENNA 1 mg hard capsules

High-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat inductionseal (HIS) liner, containing 30 hard capsules.

Not all packs may be marketed.

## 6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with localrequirements.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacisthow to dispose of medicines no longer required. These measures will help to protect the environment.

## 7. Marketing Authorization Holder

Excella GmbH & Co. KGNürberger Strasse 12

90537,

Feucht

Germany

### 8. Marketing Authorization number

TAN 22 HM 0113

### 9. Date of first Authorization.

11/04/2022

### 10. Date of revision of the text.

April, 2022