PFIZER
TALZENNA
(Talazoparib)

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 hard capsule contains talazoparib tosylate equivalent to 0.25 mg talazoparib.

Talzenna 1 mg hard capsules

Each hard capsule contains talazoparib tosylate equivalent to 1 mg talazoparib.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Talzenna 0.25 mg hard capsules

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

Talzenna 1 mg hard capsules

Opaque, size #4 hard 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 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 Pharmacodynamic properties). 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.

4.2 Posology and method of administration

Treatment with Talzenna should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Patients should be selected for the treatment of breast cancer with Talzenna based on the presence of deleterious or suspected deleterious germline BRCA mutations determined by an experienced

laboratory using a validated test method.

Genetic counselling for patients with BRCA mutations should be performed according to local regulations, as applicable.

Posology

The recommended dose is 1 mg talazoparib once daily. Patients should be treated until disease progression or unacceptable toxicity occurs.

Missing dose
If the patient vomits or misses a dose of Talzenna, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

Dose adjustments
To manage adverse drug reactions, interruption of treatment or dose reduction based on severity and clinical presentation should be considered (Table 2). Recommended dose reductions are indicated in Table 1.

Table 1. Dose adjustments 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 monitored monthly and as clinically indicated (see Table 2 and section 4.4 Special warnings and precautions for use).

Table 2. Dose modification and management

	Withhold Talzenna until levels resolve to	**Resume Talzenna**
Haemoglobin <8 g/dL	≥9 g/dL	Resume Talzenna at next lower dose
Platelet count <50,000/µL	≥75,000/µL	
Neutrophil count <1,000/µL	≥1,500/µL	
Non-haematologic adverse reaction Grade 3 or Grade 4	≤Grade 1	Consider resuming Talzenna at next lower 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 should only be considered after careful evaluation of the potential benefits and risks. If co-administration 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 Interaction with other medicinal products and other forms of interaction).

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), moderate hepatic impairment (total bilirubin >1.5 to 3.0 × ULN and any AST) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST) (see section 5.2 Pharmacokinetic properties).

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 starting dose of Talzenna is 0.75 mg once daily. For patients with severe renal impairment (15 mL/min ≤ CrCL < 30 mL/min), the recommended starting dose of Talzenna is 0.5 mg once daily. Talzenna has not been studied in patients with CrCL < 15 mL/min or patients requiring haemodialysis (see section 5.2 Pharmacokinetic properties).

Elderly
No dose adjustment is necessary in elderly (≥65 years of age) patients (see section 5.2 Pharmacokinetic properties).

Paediatric population
The safety and efficacy of Talzenna in children and adolescents <18 years of age have not been established. No data are available.

Method of administration

Talzenna is for oral use. To avoid contact with the capsule content, the capsules should be swallowed whole, and must not be opened or dissolved. They can be taken with or without food (see section 5.2 Pharmacokinetic properties).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 List of excipients.

Breast-feeding (see section 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use

Myelosuppression

Myelosuppression consisting of anaemia, leukopenia/neutropenia, and/or thrombocytopenia, have been reported in patients treated with talazoparib (see section 4.8 Undesirable effects). Talazoparib should not be started until patients have recovered from haematological toxicity caused by previous therapy (≤Grade 1).

Precautions should be taken to routinely monitor haematology parameters and signs and symptoms associated with anaemia, leukopenia/neutropenia, and/or thrombocytopenia in patients receiving talazoparib. If such events occur, dose modifications (reduction or interruption) are recommended (see section 4.2 Posology and method of administration). 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 leukaemia

Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in patients who received poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors,

including talazoparib. Overall, MDS/AML has been reported in < 1% of solid tumour patients treated with talazoparib in clinical studies (see section 4.8 Undesirable effects). 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 haematologic toxicity during treatment. If MDS/AML is confirmed, talazoparib should be discontinued.

Contraception in women of childbearing potential

Talazoparib was clastogenic in an *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes and in an *in vivo* bone marrow micronucleus assay in rats but not mutagenic in Ames assay (see section 5.3 Preclinical safety data), and may cause foetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus (see section 4.6 Fertility, pregnancy and lactation). Women of childbearing potential should not become pregnant while receiving Talzenna and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment.

A highly effective method of contraception is required for female patients during treatment with Talzenna, and for at least 7 months after completing therapy. Since the use of hormonal contraception is not recommended in patients with breast cancer, two non-hormonal and complementary contraception methods should be used (see section 4.6 Fertility, pregnancy and lactation).

Male patients with female partners of reproductive potential or pregnant partners should be advised 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 breast cancer resistance protein (BCRP) and it is mainly eliminated by renal clearance as unchanged compound.

Agents that may affect talazoparib plasma concentrations

P-gp inhibitors
Data from a drug-drug interaction study in patients with advanced solid tumours indicated that co-administration 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 also shown that concomitant use of strong P-gp inhibitors increased talazoparib exposure by 45%, relative to talazoparib given alone.

Concomitant use of strong P-gp inhibitors (including but not limited to amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, and verapamil) should be avoided. If co-administration with a strong P-gp inhibitor is unavoidable, the Talzenna dose should be reduced (see section 4.2 Posology and method of administration).

P-gp inducers
Data from a drug-drug interaction study in patients with advanced solid tumours indicated that co-administration of single 1 mg talazoparib dose with multiple daily doses of a P-gp inducer, rifampin 600 mg, with rifampin co-administered 30 minutes before talazoparib on the day of

talazoparib dosing, increased talazoparib C_{max} by approximately 37% whereas AUC_{inf} was not affected relative to a single 1 mg talazoparib dose administered alone. This is probably the net effect of both P-gp induction and inhibition by rifampin under the tested conditions in the drug-drug interaction study. No talazoparib dose adjustments are required when co-administered with rifampin. However, the effect of other P-gp inducers on talazoparib exposure has not been studied. Other P-gp inducers (including but not limited to carbamazepine, phenytoin, and St. John's wort) may decrease talazoparib exposure.

BCRP inhibitors
The effect of BCRP inhibitors on PK of talazoparib has not been studied *in vivo*. Co-administration of talazoparib with BCRP inhibitors may increase talazoparib exposure. Concomitant use of strong BCRP inhibitors (including but not limited to curcumin and cyclosporine) should be avoided. If co-administration of strong BCRP inhibitors cannot be avoided, patient should be monitored for potential increased adverse reactions.

Effect of acid-reducing agents
Population PK analysis indicates that co-administration of acid-reducing agents including proton pump inhibitors and histamine receptor 2 antagonists (H_2RA), or other acid-reducing agents had no significant impact on the absorption of talazoparib.

Systemic hormonal contraception
Drug-drug interaction studies between talazoparib and oral contraceptives have not been conducted.

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 and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment (see section 4.4 Special warnings and precautions for use).

Women of childbearing potential must use highly effective forms of contraception (see section 4.4 Special warnings and precautions for use) prior to starting treatment with talazoparib, during treatment, and for 7 months after stopping treatment with talazoparib. Since the use of hormonal contraception is not recommended in patients with breast cancer, two non-hormonal and complementary contraception methods should be used. Male patients with female partners of reproductive potential or pregnant partners should be advised to use effective contraception (even after vasectomy) during treatment with Talzenna, and for at least 4 months after the final dose (see section 4.4 Special warnings and precautions for use).

Pregnancy

There are no data from the use of Talzenna in pregnant women. Studies in animals have shown embryo-foetal toxicity (see section 5.3 Preclinical safety data). Talzenna may cause foetal harm when administered to a pregnant woman. Talzenna is not recommended during pregnancy or for women of childbearing potential not using contraception (see section 4.4 Special warnings and precautions for use).

Breast-feeding

It is unknown whether talazoparib is excreted in human breast milk. A risk to breast-fed children cannot be excluded and therefore breast-feeding is contraindicated (see section 4.3 Contraindications) during treatment 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 (partially reversible) and ovary (reversible), Talzenna may impair fertility in males of reproductive potential (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Talzenna has a minor influence on the ability to drive and use machines. Fatigue/asthenia or dizziness may occur following administration of talazoparib.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of Talzenna is based on pooled data from 1 088 patients, including 690 patients who received talazoparib monotherapy at 1 mg daily in clinical studies for solid tumours and 398 patients with mCRPC who received talazoparib 0.5 mg in combination with enzalutamide 160 mg in the TALAPRO-2 study.

The most common (≥20%) adverse reactions in patients receiving talazoparib in these clinical studies were anaemia (55.6%), fatigue (52.5%), nausea (35.8%), neutropenia (30.3%), thrombocytopenia (25.2%) and decreased appetite (21.1%). The most common (≥10%) Grade ≥3 adverse reactions of talazoparib were anaemia (39.2%), neutropenia (16.5%) and thrombocytopenia (11.1%).

Dose modifications (dose reductions or dose interruptions) due to any adverse reaction occurred in 58.7% of patients receiving Talzenna 1 mg monotherapy. The most common adverse reactions leading to dose modifications were anaemia (33.5%), neutropenia (11.7%) and thrombocytopenia (9.9%). Permanent discontinuation due to an adverse reaction occurred in 2.9% of patients receiving Talzenna; the most common was anaemia (0.6%). The median duration of exposure was 5.6 months (range 0.0 to 70.2).

Dose interruptions of Talzenna due to adverse reactions occurred in 62.1% of patients with mCRPC receiving Talzenna in combination with enzalutamide; the most common was anaemia (44%). Dose reductions of Talzenna due to adverse reactions occurred in 52.8% of patients; the most common was anaemia (43.2%). Permanent discontinuation of Talzenna due to adverse reactions occurred in 18.8% of patients; the most common was anaemia (8.3%). The median duration of talazoparib exposure was 86 weeks (range 0.29 to 186.14).

Tabulated list of adverse reactions

Table 3 summarises adverse reactions based on pooled dataset listed by system organ class, and frequency category. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10) and uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions based on pooled dataset from 8 studies (N=1 088)

System organ class **Frequency** **Preferred term**	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Uncommon			
Myelodysplastic syndrome/Acute myeloid leukaemia[a]	2 (0.2)	1 (< 0.1)	1 (< 0.1)
Blood and lymphatic system disorders			
Very common			
Thrombocytopenia[b]	274 (25.2)	88 (8.1)	33 (3.0)
Anaemia[c]	605 (55.6)	411 (37.8)	16 (1.5)
Neutropenia[d]	330 (30.3)	163 (15.0)	17 (1.6)
Leukopenia[e]	195 (17.9)	52 (4.8)	2 (0.2)
Common			
Lymphopenia[f]	88 (8.1)	37 (3.4)	4 (0.4)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	230 (21.1)	11 (1.0)	0 (0.0)
Nervous system disorders			
Very common			
Dizziness	157 (14.4)	4 (0.4)	1 (< 0.1)
Headache	207 (19.0)	8 (0.7)	N/A
Common			
Dysgeusia	68 (6.3)	0 (0.0)	0 (0.0)
Gastrointestinal disorders			
Very common			
Vomiting	167 (15.3)	9 (0.8)	0 (0.0)
Diarrhoea	205 (18.8)	4 (0.4)	0 (0.0)
Nausea	389 (35.8)	10 (0.9)	N/A
Abdominal pain[g]	162 (14.9)	12 (1.1)	N/A
Common			
Stomatitis	54 (5.0)	0 (0.0)	0 (0.0)
Dyspepsia	69 (6.3)	0 (0.0)	N/A
Skin and subcutaneous tissue disorders			
Very common			
Alopecia	189 (17.4)	N/A	N/A
General disorders and administration site conditions			
Very common			
Fatigue[h]	571 (52.5)	58 (5.3)	N/A

Abbreviations: n=number of patients; N/A=not applicable.

a. See also section 4.4 Special warnings and precautions for use.
b. Includes preferred terms of thrombocytopenia and platelet count decreased.
c. Includes preferred terms of anaemia, haematocrit decreased, haemoglobin decreased and red blood cell count decreased.
d. Includes preferred terms of neutropenia and neutrophil count decreased.
e. Includes preferred terms of leukopenia and white blood cell count decreased.
f. Includes preferred terms of lymphocyte count decreased and lymphopenia.
g. Includes preferred terms of abdominal pain, abdominal pain upper, abdominal discomfort and abdominal pain lower.
h. Includes preferred terms of fatigue and asthenia.

Description of selected adverse reactions

Myelosuppression
Myelosuppression-related adverse reactions of anaemia, neutropenia and thrombocytopenia were very commonly reported in patients treated with talazoparib. Grade 3 and Grade 4 myelosuppression-related events were reported for anaemia in 37.8% and 1.5% of patients, neutropenia in 15.0% and 1.6%, and thrombocytopenia in 8.1% and 3.0%. No deaths were reported due to myelosuppression-related adverse reactions.

In monotherapy studies (1 mg/day population), the most frequent myelosuppression-related adverse events associated with dose modifications were anaemia (33.5%), neutropenia (11.7%) and thrombocytopenia (9.9%) reported for up to approximately 30% of patients in the talazoparib 1 mg/day population and the one associated with permanent study drug discontinuation was anaemia reported in 0.6% of patients.

In patients with mCRPC treated with talazoparib in combination with enzalutamide, anaemia led to talazoparib dose interruption in 44.0% of patients, decreased neutrophil count in 13.6%, and decreased platelet count in 7.8%. Overall, 42.5% of patients required blood transfusions. The most common blood transfusion was of packed red blood cells 39.2%. Discontinuation due to anaemia, neutropenia and thrombocytopenia occurred, respectively, in 8.3%, 3.3% and 0.5% of patients.

4.9 Overdose

There is limited experience of overdose with talazoparib. No adverse reactions were reported in one patient who accidentally self-administered thirty 1 mg capsules of talazoparib on Day 1 and was immediately treated with gastric decontamination. 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

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XK04

Mechanism of action

Talazoparib is an inhibitor of PARP enzymes, PARP1 (IC_{50}=0.7 nM), and PARP2 (IC_{50}=0.3 nM). PARP enzymes are involved in cellular DNA damage response signalling pathways such as DNA repair, gene transcription, 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, thereby resulting in apoptosis and/or cell death. Treatment of cancer cell lines that are harbouring defects in DNA repair genes with talazoparib single agent leads to increased levels of γH2AX, a marker of double stranded DNA breaks, and results in decreased cell proliferation and increased apoptosis. Talazoparib anti-tumour activity was also observed in a patient-derived xenograft (PDX) BRCA mutant breast cancer model where the patient was previously treated with a platinum-based regimen. In this PDX model talazoparib decreased tumour growth and increased γH2AX level and apoptosis in the tumours.

Cardiac electrophysiology

The effect of talazoparib on cardiac repolarisation 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 tumours. Talazoparib did not have a clinically relevant effect on QTc prolongation at the maximum clinically recommended monotherapy dose of 1 mg once daily.

Clinical efficacy and safety

Germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer

EMBRACA study
EMBRACA was an open-label, randomised, parallel, 2-arm multicentre 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 PARPi was permitted.

Of the 431 patients randomised in the EMBRACA study, 408 (95%) were centrally confirmed to have a deleterious or suspected deleterious gBRCAm using a clinical study assay; out of which 354 (82%) were confirmed using the BRACAnalysis CDx. BRCA mutation status (breast cancer susceptibility gene 1 [BRCA1] positive or breast cancer susceptibility gene 2 [BRCA2] positive) was similar across both treatment arms.

A total of 431 patients were randomised 2:1 to receive Talzenna 1 mg capsules once daily or chemotherapy at standard doses until progression or unacceptable toxicity. Of the 431 patients randomised onto EMBRACA, 287 were randomised to the Talzenna arm and 144 to the chemotherapy arm. Randomisation 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).

Patient demographic, baseline, and disease characteristics were generally similar between the study treatment arms (see Table 4).

Table 4. Demographic, baseline, and disease characteristics – EMBRACA study

	Talazoparib (N=287)	**Chemotherapy (N=144)**
Median age (y [range])	45.0 (27.0, 84.0)	50.0 (24.0, 88.0)
Age category (y), n (%)		
<50	182 (63.4%)	67 (46.5%)
50 to <65	78 (27.2%)	67 (46.5%)
≥ 65	27 (9.4%)	10 (6.9%)
Gender, n (%)		
Female	283 (98.6%)	141 (97.9%)
Male	4 (1.4%)	3 (2.1%)
Race, n (%)		
Asian	31 (10.8%)	16 (11.1%)
Black or African American	12 (4.2%)	1 (0.7%)
White	192 (66.9%)	108 (75.0%)
Other	5 (1.7%)	1 (0.7%)
Not reported	47 (16.4%)	18 (12.5%)
ECOG performance status, n (%)		

Table 4. Demographic, baseline, and disease characteristics – EMBRACA study

	Talazoparib (N=287)	Chemotherapy (N=144)
0	153 (53.3%)	84 (58.3%)
1	127 (44.3%)	57 (39.6%)
2	6 (2.1%)	2 (1.4%)
Missing	1 (0.3%)	1 (0.7%)
Hormone receptor status, n (%)		
HER2-positive	0 (0.0%)	0 (0.0%)
Triple-negative	130 (45.3%)	60 (41.7%)
Hormone receptor-positive (ER positive or PgR positive)	157 (54.7%)	84 (58.3%)
BRCA status by central or local laboratory assessment, n (%)	287 (100.0%)	144 (100.0%)
BRCA1-mutation positive	133 (46.3%)	63 (43.8%)
BRCA2-mutation positive	154 (53.7%)	81 (56.3%)
Time from initial diagnosis of breast cancer to diagnosis of advanced breast cancer (years)		
n	286	144
Median	1.9	2.7
Minimum, maximum	0, 22	0, 24
Categories for time from initial diagnosis of breast cancer to diagnosis of advanced breast cancer		
<12 months	108 (37.6%)	42 (29.2%)
≥12 months	178 (62.0%)	102 (70.8%)
Number of prior cytotoxic regimens for locally advanced or metastatic disease		
Mean (Std Dev)	0.9 (1.01)	0.9 (0.89)
Median	1	1
Minimum, maximum	0, 4	0, 3
Number of patients who received prior cytotoxic regimens for locally advanced or metastatic disease, n (%)		
0	111 (38.7%)	54 (37.5%)
1	107 (37.3%)	54 (37.5%)
2	57 (19.9%)	28 (19.4%)
3	11 (3.8%)	8 (5.6%)
≥4	1 (0.3%)	0 (0.0%)
Number of patients who received following prior therapies, n (%)		
Taxane	262 (91.3%)	130 (90.3%)
Anthracycline	243 (84.7%)	115 (79.9%)
Platinum	46 (16.0%)	30 (20.8%)

Abbreviations: BRCA=breast cancer susceptibility gene; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; N=number of patients; n=number of patients in category; PgR=progesterone receptor.

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.

The study demonstrated a statistically significant improvement in PFS, the primary efficacy outcome, for Talzenna compared with chemotherapy. There was no statistically significant effect on OS at the time of final OS analysis. Efficacy data for EMBRACA are summarised in Table 5. The Kaplan-Meier curves for PFS and OS are displayed in Figure 1 and Figure 3, respectively.

Table 5. Summary of efficacy results – EMBRACA study*

	Talazoparib	Chemotherapy
PFS 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[a] (95% CI)	0.54 (0.41, 0.71)	
2-sided p-value[b]	p<0.0001	
OS (final analysis)[c]	N=287	N=144
Events, number (%)	216 (75.3%)	108 (75%)
Median (95% CI), months	19.3 (16.6, 22.5)	19.5 (17.4, 22.4)
Hazard ratio[a] (95% CI)	0.85 (0.67, 1.07)[c]	
2-sided p-value[b]	p=0.1693	
Objective response by investigator[d,e]	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 (2.93, 8.83)	
2-sided p-value[f]	p<0.0001	
Duration of response by investigator[d]	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; N=number of patients; ORR=objective response rate; OS=overall survival; PARP=poly (adenosine diphosphate-ribose) polymerase; PFS=progression-free survival; PR=partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

* PFS, ORR and Duration of response are based on the data cutoff date of 15 September 2017 and a median follow-up for PFS of 13.0 months (95% CI: 11.1, 18.4) in the talazoparib arm and 7.2 months (95% CI: 4.6, 11.1) in the chemotherapy arm. OS is based on the data cutoff date 30 September 2019, and a median follow-up of 44.9 months (95% CI: 37.9, 47.0) in the talazoparib arm and 36.8 months (95% CI: 34.3, 43.0) in the chemotherapy arm.

a. 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 favouring talazoparib.

b. Stratified log-rank test.

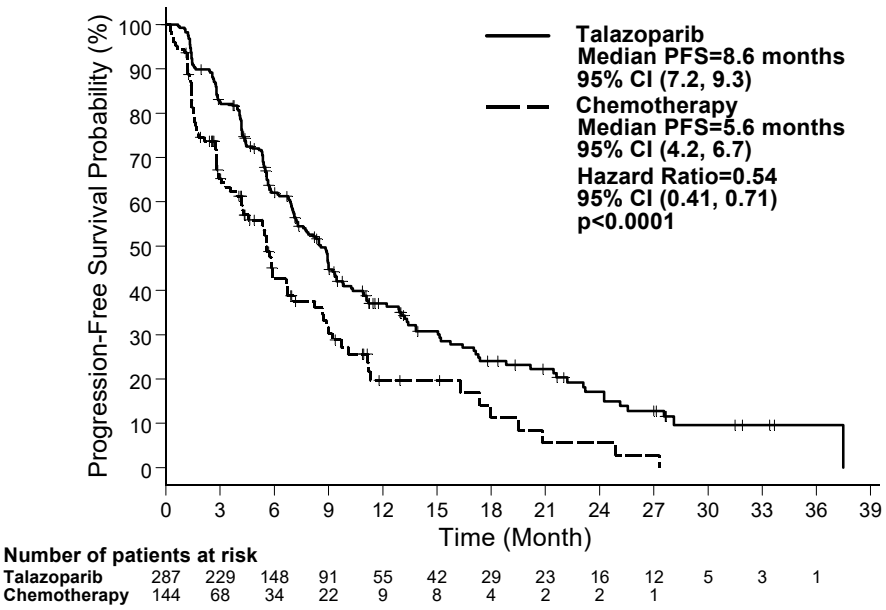
c. At the time of the final OS analysis, 46.3% versus 41.7% of patients randomised in the talazoparib and chemotherapy arms, respectively, received subsequently a platinum therapy, and 4.5% versus 32.6% received subsequently a PARP inhibitor treatment.

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

e. Per RECIST 1.1, confirmation of CR/PR was not required.

f. Stratified CMH test.

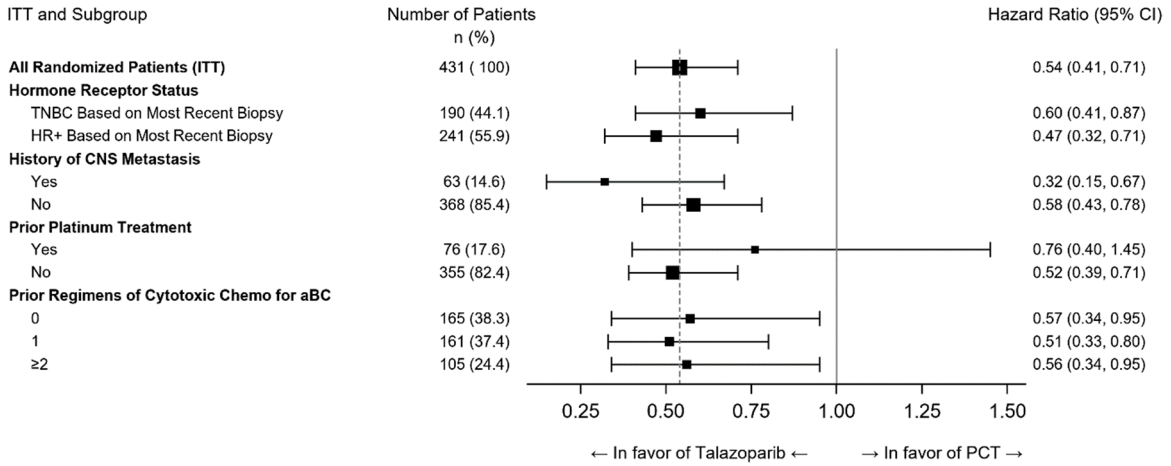
Figure 1. Kaplan-Meier curves of PFS—EMBRACA study



Abbreviations: CI=confidence interval; PFS=progression-free survival.

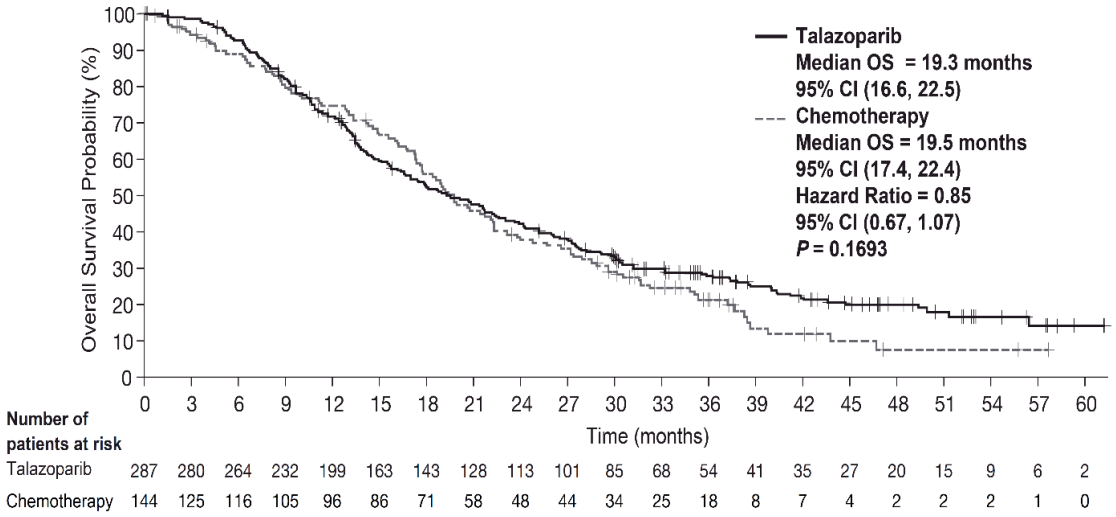
A series of prespecified subgroup PFS analyses was performed based on prognostic factors and baseline characteristics to investigate the internal consistency of treatment effect. Consistent with the overall results, a reduction in the risk of disease progression or death in favour of the talazoparib arm was observed in all individual patient subgroups (Figure 2).

Figure 2. Forest plot of PFS analyses for key subgroups—EMBRACA study



Abbreviations: aBC=advanced breast cancer; CI=confidence interval; CNS=central nervous system; HR+=hormone receptor-positive; ITT=intent-to-treat; PCT=physician's choice treatment (chemotherapy); PFS=progression-free survival; TNBC=triple-negative breast cancer.

Figure 3. Kaplan-Meier curves of overall survival—EMBRACA study



Abbreviations: CI=confidence interval; OS=overall survival.
Primary analysis' p-value was based on a stratified log-rank test.

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 (% coefficient of variation [CV%]) 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 (107) ng•h/mL to 208 (37) ng•h/mL and 11 (90) ng/mL to 19 (27) ng/mL, respectively. Following repeated daily dosing, plasma talazoparib 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 2.3 to 5.2. Talazoparib is a substrate of P-gp and BCRP transporters.

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 41% with fraction absorbed of at least 69% (see Elimination). No significant effect of acid-reducing agents on talazoparib exposure is expected, given sufficient solubility of talazoparib at all pHs between 1 and 6.8. Twenty-eight percent (28%) of the patients in the pivotal study were taking acid-reducing agents, mainly proton pump inhibitors.

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 (see section 4.2 Posology and method of administration).

Distribution

The population mean 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 or hepatic 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 or hepatic function.

Biotransformation

Talazoparib undergoes minimal hepatic metabolism in humans. Following oral administration of a single 1 mg dose of [^{14}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 faeces.

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 salt export 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

Renal elimination of unchanged drug (passive filtration and active secretion) is the major route of talazoparib elimination. P-gp is likely involved in talazoparib active renal secretion. The mean (±standard deviation) terminal plasma half-life of talazoparib was 90 (±58) hours and the population mean (inter-subject variability) apparent oral clearance (CL/F) was 6.5 (31%) L/h in cancer patients. In 6 female patients given a single oral dose of [^{14}C] talazoparib, a mean of 69% (±8.6%) and 20% (±5.5%) of the total administered radioactive dose was recovered in urine and faeces, respectively. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 55% of the administered dose, while unchanged talazoparib recovered in the faeces accounted for 14%.

Special populations

Age, sex, and body weight
A population PK analysis was conducted using data from 490 patients with cancer who received talazoparib 1 mg daily as monotherapy to evaluate the impact of age (ranging from 18 to 88 years), sex (53 males and 437 females), and body weight (ranging from 35.7 kg to 162 kg) on the PK of talazoparib. The results have shown that age, sex, and body weight had no clinically relevant effect on the PK of talazoparib.

Race
Based on a population PK analysis that included 490 patients who received talazoparib 1 mg daily as monotherapy, where 41 patients were Asian and 449 patients were Non-Asian (361 White, 16 Black, 9 Others, and 63 Not reported), talazoparib CL/F was higher in Asian patients compared to Non-Asian patients, leading to 19% lower exposure (AUC) in Asian patients.

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

Renal impairment
Data from a PK study in advanced cancer patients with varying degrees of renal impairment indicated that talazoparib total exposure (AUC_{0-24}) after multiple talazoparib once daily doses

increased by 92% and 169% in patients with moderate (eGFR 30 – < 60 mL/min) and severe (eGFR < 30 mL/min) renal impairment, respectively, relative to patients with normal renal function (eGFR ≥ 90 mL/min). Talazoparib C_{max} increased by 90% and 107% in patients with moderate and severe renal impairment, respectively, relative to patients with normal renal function. Talazoparib exposure was similar for patients with mild renal impairment (eGFR 60 – < 90 mL/min) and those with normal renal function. In addition, based on 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), talazoparib CL/F was decreased by 14% and 37% 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 have not been studied in patients requiring haemodialysis (see section 4.2 Posology and method of administration).

Hepatic impairment
Based on a population PK analysis that included 490 patients who received talazoparib 1 mg daily as monotherapy, 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 in patients with normal hepatic function, mild hepatic impairment, moderate hepatic impairment (total bilirubin > 1.5 to 3.0 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3.0 × ULN and any AST) was studied in a PK study. Population PK analysis using data from this PK study indicated that mild, moderate or severe hepatic impairment had no significant impact on the PK of talazoparib (see section 4.2 Posology and method of administration).

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 lymphocytes and 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 in rats and in dogs, the main findings at subtherapeutic exposures included bone marrow hypocellularity with dose-dependent decrease in haematopoietic 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 with the pharmacology of talazoparib and its tissue distribution pattern.

Developmental toxicology

In an embryo-foetal development study in rats, talazoparib resulted in embryo-foetal death, foetal malformation (depressed eye bulge, small eye, split sternebrae, 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

Capsule content

Silicified microcrystalline cellulose (microcrystalline cellulose and silicone dioxide)

0.25 mg capsule shell

Hypromellose
Yellow iron oxide (E172)
Titanium dioxide (E171)

1 mg capsule shell

Hypromellose
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)

Printing ink

Shellac (NF)
Dehydrated Alcohol (USP)
Isopropyl Alcohol (USP)
Butyl Alcohol (NF)
Propylene Glycol (USP)
Strong Ammonia Solution (NF)
Black iron oxide (NF)
Potassium Hydroxide (NF)
Purified Water (USP)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store below 30°C.

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 liner. Pack size: cartons of 30 capsules in a HDPE bottle.

Polyvinyl chloride/polyvinylidene chloride (PVC/PVdC) perforated unit dose blister with an

aluminum peel off foil lidding. Pack sizes: cartons of 30 × 1 capsules, or 60 × 1 capsules, or 90 × 1 capsules in unit dose blisters.

Talzenna 1 mg hard capsules

High-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat induction seal liner. Pack size: cartons of 30 capsules in a HDPE bottle.

Polyvinyl chloride/polyvinylidene chloride (PVC/PVdC) perforated unit dose blister with an aluminum peel off foil lidding. Pack size: cartons of 30 × 1 capsules in unit dose blisters.

Some product strengths or pack sizes may not be available in your country.

6.6 Special precautions for disposal

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

7. MANUFACTURER

Excella GmbH & Co. KG,
Nurnburger Strasse 12,
90537 Feucht, Germany.

Date of Revision: 02 MAY 2024

TALZENNA-0524