ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Talzenna 0.25 mg hard capsules

Opaque, approximately 14.30 mm x 5.32 mm 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, approximately 14.30 mm x 5.32 mm 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). 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, 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 (see 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).

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).

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).

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).

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

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).

4.3 Contraindications

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

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Myelosuppression

Myelosuppression consisting of anaemia, leucopenia/neutropenia, and/or thrombocytopenia, have been reported in patients treated with talazoparib (see section 4.8). 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, leucopenia/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 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. 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), 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). 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).

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).

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).

Women of childbearing potential must use highly effective forms of contraception (see section 4.4) 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).

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). 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).

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 not recommended 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).

4.7 Effects on ability to drive and use machines

Talzenna may have 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 494 patients who received talazoparib at 1 mg daily in clinical studies for solid tumours, including 286 patients from a randomised Phase 3 study with germline BRCA-mutated (gBRCAm), HER2-negative locally

advanced or metastatic breast cancer and 83 patients from a nonrandomised 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 adverse reactions 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).

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) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions based on pooled dataset from 5 studies (N=494)

System organ class **Frequency** **Preferred term**	**All grades*** **n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Blood and lymphatic system disorders			
Very common			
Thrombocytopenia[a]	146 (29.6)	63 (12.8)	20 (4.0)
Anaemia[b]	245 (49.6)	172 (34.8)	2 (0.4)
Neutropenia[c]	149 (30.2)	77 (15.6)	9 (1.8)
Leucopenia[d]	77 (15.6)	24 (4.9)	1 (0.2)
Common			
Lymphopenia[e]	30 (6.1)	13 (2.6)	0 (0.0)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	100 (20.2)	2 (0.4)	0 (0.0)
Nervous system disorders			
Very common			
Dizziness	69 (14.0)	1 (0.2)	N/A
Headache	131 (26.5)	5 (1.0)	N/A
Common			
Dysgeusia	42 (8.5)	0 (0.0)	0 (0.0)
Gastrointestinal disorders			
Very common			
Vomiting	110 (22.3)	7 (1.4)	0 (0.0)
Diarrhoea	112 (22.7)	3 (0.6)	0 (0.0)
Nausea	219 (44.3)	4 (0.8)	N/A
Abdominal pain[f]	105 (21.3)	8 (1.6)	N/A
Common			
Stomatitis	32 (6.5)	0 (0.0)	0 (0.0)
Dyspepsia	41 (8.3)	0 (0.0)	N/A
Skin and subcutaneous tissue disorders			
Very common			
Alopecia[g]	110 (22.3)	N/A	N/A

Table 3. Adverse reactions based on pooled dataset from 5 studies (N=494)

System organ class Frequency Preferred term	All grades* n (%)	Grade 3 n (%)	Grade 4 n (%)
General disorders and administration site conditions			
Very common			
Fatigue[h]	282 (57.1)	17 (3.4)	1 (0.2)

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

* There were no Grade 5 adverse drug reactions.

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

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

c. Includes preferred terms of neutropenia and neutrophil count decreased.

d. Includes preferred terms of leucopenia 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 abdominal pain lower.

g. For talazoparib Grade 1 is 21% and Grade 2 is 2%.

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 1 mg/day. Grade 3 and Grade 4 myelosuppression-related events were reported for anaemia 34.8% and 0.4%, neutropenia 15.6% and 1.8%, and thrombocytopenia 12.8% and 4.0%. No deaths were reported due to myelosuppression-related adverse reactions. Myelosuppression-related adverse events associated with dose modifications were reported for up to approximately 30% of patients in the talazoparib 1 mg/day population and those associated with permanent study drug discontinuation were reported for less than 1% of patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after 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 via the national reporting system listed in Appendix V.

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: other antineoplastic agents, ATC code: L01XK04

Mechanism of action

Talazoparib is an inhibitor of PARP enzymes, PARP1, and PARP2. 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 dose of 1 mg once daily.

Clinical efficacy and safety

Randomised phase 3 study EMBRACA
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 PARP inhibitor 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 trial 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 (%)		
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; 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.

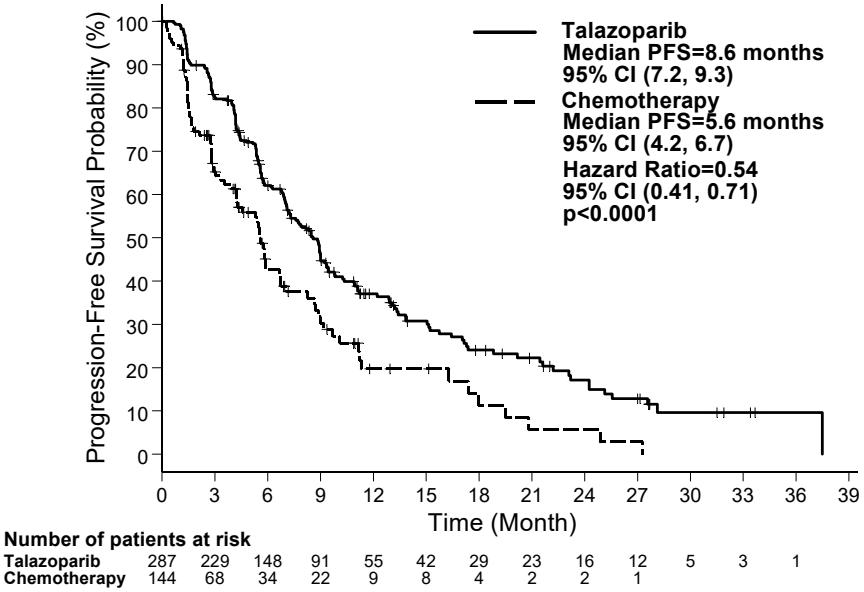
[c.] At the time of the final OS analysis, 46.3% versus 41.7% of patients randomised in the talazoparib and chemotherapy arms, respectively, received subsequently a platinum therapy, and 4.5% versus 32.6% received subsequently a PARP inhibitor treatment.

[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.

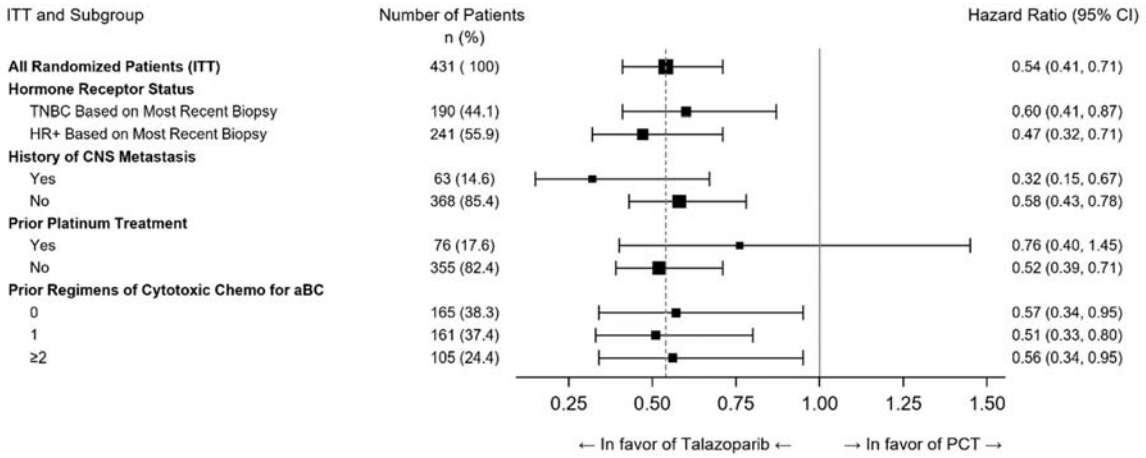
Figure 1. Kaplan-Meier curves of PFS – EMBRACA study



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

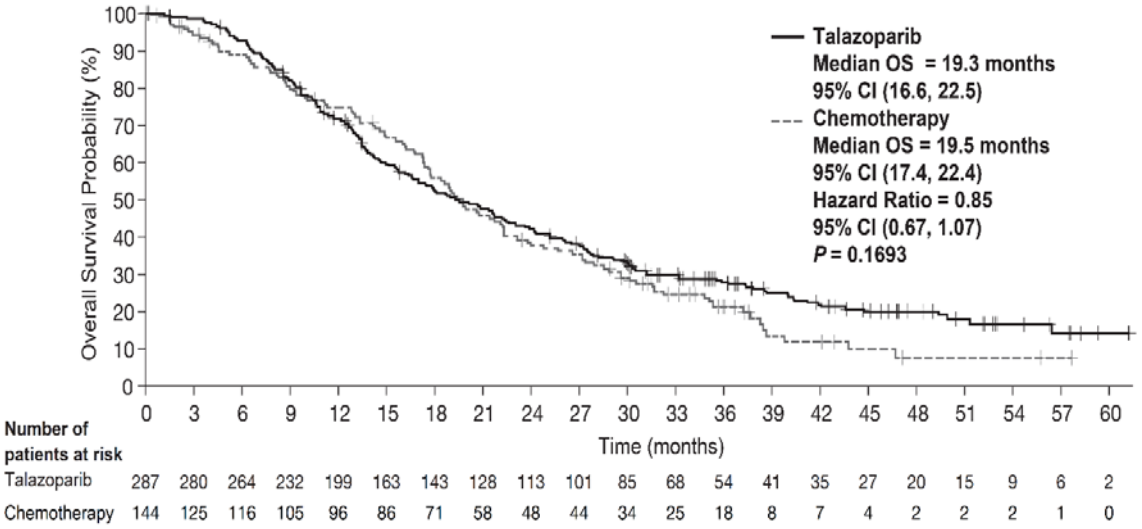
A series of prespecified subgroup PFS analyses was performed based on prognostic factors and baseline characteristics to investigate the internal consistency of treatment effect. Consistent with the overall results, a reduction in the risk of disease progression or death in favour of the talazoparib 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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with talazoparib in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

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•hr/mL to 208 (37) ng•hr/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).

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%.

Age, sex, 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), 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, 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 trial 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).

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 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 trial. Population PK analysis using data from this PK trial indicated that mild, moderate or severe hepatic impairment had no significant impact on the PK of talazoparib (see section 4.2).

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 (sMCC) (microcrystalline cellulose and silicone dioxide)

0.25 mg capsule shell

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

1 mg capsule shell

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

Printing ink

Shellac (E904)
Propylene glycol (E1520)
Ammonium hydroxide (E527)
Black iron oxide (E172)
Potassium hydroxide (E525)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

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 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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Talzenna 0.25 mg hard capsules

EU/1/19/1377/001
EU/1/19/1377/002
EU/1/19/1377/003
EU/1/19/1377/004

Talzenna 1 mg hard capsules

EU/1/19/1377/005
EU/1/19/1377/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Excella GmbH & Co. KG
Nürnberger Str. 12
90537 Feucht
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Talzenna 0.25 mg hard capsules
talazoparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains talazoparib tosylate equivalent to 0.25 mg talazoparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
30 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow whole. Do not open, crush or chew the capsules.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1377/001 (30 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Talzenna 0.25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Talzenna 0.25 mg hard capsules
talazoparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains talazoparib tosylate equivalent to 0.25 mg talazoparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
30 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use. Swallow whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1377/001 (30 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Talzenna 0.25 mg hard capsules
talazoparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains talazoparib tosylate equivalent to 0.25 mg talazoparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
30 × 1 capsules
60 × 1 capsules
90 × 1 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow whole. Do not open, crush or chew the capsules.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1377/002 (30 hard capsules)
EU/1/19/1377/003 (60 hard capsules)
EU/1/19/1377/004 (90 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Talzenna 0.25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Talzenna 0.25 mg capsules
talazoparib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Talzenna 1 mg hard capsules
talazoparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains talazoparib tosylate equivalent to 1 mg talazoparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
30 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow whole. Do not open, crush or chew the capsules.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1377/005 (30 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Talzenna 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Talzenna 1 mg hard capsules
talazoparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains talazoparib tosylate equivalent to 1 mg talazoparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
30 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use. Swallow whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1377/005 (30 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Talzenna 1 mg hard capsules
talazoparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains talazoparib tosylate equivalent to 1 mg talazoparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
30 × 1 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow whole. Do not open, crush or chew the capsules.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1377/006 (30 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Talzenna 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Talzenna 1 mg capsules
talazoparib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Talzenna 0.25 mg hard capsules
Talzenna 1 mg hard capsules
talazoparib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Talzenna is and what it is used for

What Talzenna is and how it works
Talzenna contains the active substance talazoparib. It is a type of anticancer medicine known as a 'PARP (poly-ADP ribose polymerase) inhibitor'.

Patients with changes (mutations) in genes called BRCA are at risk of developing some forms of cancer. Talzenna works by blocking PARP, which is an enzyme that repairs damaged DNA in certain cancer cells. As a result, the cancer cells can no longer repair themselves and they die.

What Talzenna is used for
Talzenna is used to treat adults with breast cancer of a type known as HER2-negative breast cancer who have an abnormal inherited BRCA gene.

Talzenna is used when the cancer has spread beyond the original tumour or to other parts of the body.

Your healthcare provider will perform a test to make sure that Talzenna is right for you.

If you have any questions about how Talzenna works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take Talzenna

Do not take Talzenna
- If you are allergic to talazoparib or any of the other ingredients of this medicine (listed in section 6).
- If you are breast-feeding.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Talzenna and during your treatment if you experience signs or symptoms described in this section.

Low blood cell counts
Talzenna lowers your blood cell counts, such as your red blood cell count (anaemia), white blood cell count (neutropenia), or blood platelet count (thrombocytopenia). Signs and symptoms you need to look out for include:
- **Anaemia:** Being short of breath, feeling very tired, pale skin, or fast heartbeat – these may be signs of a low red blood cell count
- **Neutropenia:** Infection, developing chills or shivering, or fever – these may be signs of a low white blood cell count
- **Thrombocytopenia:** Bruising or bleeding for longer than usual if you hurt yourself – these may be signs of a low blood platelet count

You will have regular blood tests during treatment with Talzenna to check your blood cells (white blood cells, red blood cells, and platelets).

Serious problems with the bone marrow
Rarely, low blood cell counts may be a sign of more serious problems with the bone marrow such as myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML). Your doctor may want to test your bone marrow to check for these problems.

Male and female contraception
Women who can become pregnant and men with partners who are or can become pregnant should use effective contraception.
Please see section "Male and female contraception" below.

Children and adolescents
Talzenna is not to be used in children or adolescents (under 18 years of age).

Other medicines and Talzenna
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Talzenna can affect the way some other medicines work. Also some medicines can affect the way Talzenna works.

In particular, the following may increase the risk of side effects with Talzenna:
- Amiodarone, carvedilol, dronedarone, propafenone, quinidine, ranolazine and verapamil – generally used to treat heart problems.
- Clarithromycin and erythromycin antibiotics – used to treat bacterial infections.
- Itraconazole and ketoconazole – used to treat fungal infections.
- Cobicistat, darunavir, indinavir, lopinavir, ritonavir, saquinavir, telaprevir and tipranavir used to treat HIV infections/AIDS.
- Ciclosporin – used in organ transplantation to prevent rejection.
- Lapatinib – used to treat patients with certain types of breast cancer.
- Curcumin (e.g. found in turmeric root) in some medicines (see also section Talzenna with food and drink below).

The following medicines may reduce the effect of Talzenna:
- Carbamazepine and phenytoin – anti-epileptics used to treat seizures or fits.
- St. John's wort (*Hypericum perforatum*) – a herbal remedy used to treat mild depression and anxiety.

Talzenna with food and drink
Do not use curcumin in food supplements while you are taking Talzenna as it may increase Talzenna's side effects. Curcumin is found in turmeric root and you should not use large amounts of turmeric root, but using spices in food is not likely to cause a problem.

Pregnancy
Talzenna could harm an unborn baby. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will perform a pregnancy test prior to starting Talzenna.

- You should not use Talzenna if you are pregnant.
- You should not become pregnant while taking Talzenna.
- Discuss contraception with your doctor if there is any possibility that you or your partner may become pregnant.

Male and female contraception
Women who are able to become pregnant should use effective birth control (contraception) during treatment with Talzenna and for at least 7 months after the last dose of Talzenna. Since the use of hormonal contraception is not recommended if you have breast cancer, you should use two non-hormonal contraception methods.
Talk to your healthcare provider about birth control methods that may be right for you.

Men with female partners who are pregnant or able to become pregnant should use effective birth control (contraception), even after a vasectomy, during treatment with Talzenna and for at least 4 months after the last dose.

Breast-feeding
You should not breast-feed while taking Talzenna and for at least 1 month after the last dose. It is not known if Talzenna passes into breast milk.

Fertility
Talazoparib may reduce fertility in men.

Driving and using machines
Talzenna may have a minor influence on the ability to drive and use machines. If you feel dizzy, weak, or tired (these are very common side effects of Talzenna), you should not drive or use machines.

3. How to take Talzenna

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The recommended dose is one 1-mg capsule taken by mouth once daily.

If you get certain side effects while you are taking Talzenna (see section 4), your doctor may lower your dose or stop treatment, either temporarily or permanently. The dose may be lowered to 0.75 mg (taken as three 0.25-mg capsules) once daily, or 0.5 mg (two 0.25-mg capsules) once daily, or 0.25 mg (one 0.25-mg capsule) once daily.

Swallow the capsule whole with a glass of water. Do not chew or crush the capsules. You can take Talzenna with food or between meals. Do not open the capsules. Contact with the capsule content should be avoided.

If you take more Talzenna than you should
If you have taken more Talzenna than your normal dose, contact your doctor or nearest hospital right away. Urgent treatment may be necessary.

Take the carton and this leaflet so that the doctor knows what you have been taking.

If you forget to take Talzenna
If you miss a dose or vomit, take your next dose as scheduled. Do not take a double dose to make up for the forgotten or vomited capsules.

If you stop taking Talzenna
Do not stop taking Talzenna unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following symptoms which could be a sign of serious blood disorder:

Very common (may affect more than 1 in 10 people)
- Being short of breath, feeling very tired, having pale skin, or fast heartbeat – these may be signs of a low red blood cell count (anaemia).
- Infection, developing chills or shivering, or fever or feeling hot – these may be signs of a low white blood cell count (neutropenia).
- Bruising or bleeding for longer than usual if you hurt yourself – these may be signs of a low blood platelet count (thrombocytopenia).

Talk to your doctor if you get any other side effects. These can include:

Very common (may affect more than 1 in 10 people)
- Low counts of white blood cells, red blood cells, and blood platelets
- Decreased appetite
- Feeling dizzy
- Headache
- Feeling sick (nausea)
- Being sick (vomiting)
- Diarrhoea
- Pain in the abdomen
- Hair loss

Common (may affect up to 1 in 10 people)
- Alteration in taste (dysgeusia)
- Indigestion
- Mouth inflammation

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Talzenna

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the bottle or blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Talzenna contains
- The active substance is talazoparib. Talzenna hard capsules come in different strengths.
- Talzenna 0.25 mg hard capsules: each capsule contains talazoparib tosylate equivalent to 0.25 mg talazoparib.
- Talzenna 1 mg hard capsules: each capsule contains talazoparib tosylate equivalent to 1 mg talazoparib.

The other ingredients are:
- Capsule content: silicified microcrystalline cellulose (sMCC) (microcrystalline cellulose and silicone dioxide).
- 0.25 mg capsule shell: hypromellose (HPMC), yellow iron oxide (E172), and titanium dioxide (E171)
- 1 mg capsule shell: hypromellose (HPMC), yellow iron oxide (E172), titanium dioxide (E171), and red iron oxide (E172)

Printing ink: shellac (E904), propylene glycol (E1520), ammonium hydroxide (E527), black iron oxide (E172), and potassium hydroxide (E525).

What Talzenna looks like and contents of the pack
Talzenna 0.25 mg is supplied as opaque, approximately 14.30 mm x 5.32 mm 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 is supplied as opaque, approximately 14.30 mm x 5.32 mm hard capsule with a light red cap (printed with “Pfizer” in black) and a white body (printed with “TLZ 1” in black).

Talzenna 0.25 mg is available in perforated unit dose blister packs of 30, or 60, or 90 hard capsules and in plastic bottles of 30 hard capsules.

Talzenna 1 mg is available in perforated unit dose blister packs of 30 hard capsules and in plastic bottles of 30 hard capsules.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.