FULL PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT

Talzenna® 0.25 mg
Talzenna® 1 mg

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 11.

PHARMACEUTICAL FORM

Hard capsule.

1 INDICATIONS AND USAGE

TALZENNA is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (*BRCA*)-mutated (g*BRCA*m) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of advanced breast cancer with TALZENNA based on the presence of germline *BRCA* mutations *[see Indications and Usage (1), Clinical Studies (14)]*.

2.2 Recommended Dosing

The recommended dose of TALZENNA is 1 mg taken orally once daily, with or without food.

The 0.25 mg capsule is available for dose reduction.

Patients should be treated until disease progression or unacceptable toxicity occurs.

To avoid contact with the capsule content, TALZENNA capsules should be swallowed whole, and must not be opened or dissolved.

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.

2.3 Dose Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment with or without dose reduction based on severity and clinical presentation. Recommended dose reductions are indicated in Table 1 and Table 2. Treatment with TALZENNA should be discontinued if more than three dose reductions are required.

Table 1. Dose Reduction Levels for Adverse Reactions

Dose Level	**Dose**
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

Table 2. Dose Modification and Management

Monitor complete blood counts monthly and as clinically indicated *[see Warnings and Precautions (5.2)]*.

Adverse Reactions	**Withhold TALZENNA until levels resolve to**	**Resume TALZENNA**
Hemoglobin <8 g/dL	≥9 g/dL	Resume TALZENNA at a reduced dose
Platelet count <50,000/μL	≥75,000/μL	
Neutrophil count <1,000/μL	≥1500/μL	
Non-hematologic Grade 3 or Grade 4	≤Grade 1	Consider resuming TALZENNA at a reduced dose or discontinue

2.4 Dose Modifications for Patients with Renal Impairment

For patients with moderate renal impairment (CLcr 30 - 59 mL/min), the recommended dose of TALZENNA is 0.75 mg once daily. For patients with severe renal impairment (CLcr 15 - 29 mL/min), the recommended dose of TALZENNA is 0.5 mg once daily *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

2.5 Dose Modifications for Use with P-glycoprotein (P-gp) Inhibitors

Reduce the TALZENNA dose to 0.75 mg once daily when coadministered with certain P-gp inhibitors. For additional information on interacting P-gp inhibitors, see Drug Interactions (7.1) and Clinical Pharmacology (12.3).

When the P-gp inhibitor is discontinued, increase the TALZENNA dose (after 3–5 half-lives of the P-gp inhibitor) to the dose used prior to the initiation of the P-gp inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Pediatric Use

TALZENNA is not indicated for pediatric patients.
The safety and effectiveness of TALZENNA have not been established in pediatric patients.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 0.25 mg, opaque, hard capsule with an ivory cap (printed with “Pfizer” in black) and a white body (printed with “TLZ 0.25” in black)
- 1 mg, opaque, hard capsule with a light red cap (printed with “Pfizer” in black) and a white body (printed with “TLZ 1” in black)

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with a fatal outcome, has been reported in patients who received TALZENNA.

Overall, MDS/AML has been reported in 0.4% (3 out of 788) of solid tumor patients treated with TALZENNA as a single agent in clinical studies. The durations of TALZENNA treatment in these three patients prior to developing MDS/AML was 4 months, 24 months, and 60 months respectively. These patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Do not start TALZENNA until patients have adequately recovered from hematological toxicity caused by previous chemotherapy. Monitor blood counts monthly during treatment with TALZENNA. For prolonged hematological toxicities, interrupt TALZENNA and monitor blood counts weekly until recovery. If counts do not recover within 4 weeks, refer the patient to a hematologist for further investigations including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue TALZENNA.

5.2 Myelosuppression

Myelosuppression consisting of anemia, neutropenia, and/or thrombocytopenia, have been reported in patients treated with TALZENNA *[see Adverse Reactions (6.1)]*.

Grade ≥3 anemia, neutropenia, and thrombocytopenia were reported, respectively, in 39%, 21%, and 15% of patients receiving TALZENNA as a single agent. Discontinuation due to anemia, neutropenia, and thrombocytopenia occurred, respectively, in 0.7%, 0.3%, and 0.3% of patients.

Withhold TALZENNA until patients have adequately recovered from hematological toxicity caused by previous therapy. Monitor blood counts monthly during treatment with TALZENNA. If hematological toxicities do not resolve within 28 days, discontinue TALZENNA and refer the patient to a hematologist for further investigations including bone marrow analysis and blood sample for cytogenetics *[see Dosage and Administration (2.3)]*.

5.3 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal data, TALZENNA can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, administration of talazoparib to pregnant rats during the period of organogenesis caused fetal malformations and structural skeletal variations, and

embryo-fetal death at exposures that were 0.24 times the area under the concentration-time curve (AUC) in patients receiving the recommended human dose of 1 mg daily. Apprise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of TALZENNA *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 4 months following the last dose of TALZENNA *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1)]*
- Myelosuppression *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

g*BRCA*m HER2-negative Locally Advanced or Metastatic Breast Cancer
EMBRACA
The safety of TALZENNA as a single agent was evaluated in g*BRCA*m patients with HER2-negative locally advanced or metastatic breast cancer who had previously received no more than 3 lines of chemotherapy for the treatment of locally advanced/metastatic disease *[see Clinical Studies (14.1)]*. EMBRACA was a randomized, open-label, multi-center study in which 412 patients received either TALZENNA 1 mg once daily (N=286) or a chemotherapy agent (capecitabine, eribulin, gemcitabine, or vinorelbine) of the healthcare provider's choice (N=126) until disease progression or unacceptable toxicity. The median duration of study treatment was 6.1 months in patients who received TALZENNA and 3.9 months in patients who received chemotherapy.

Serious adverse reactions of TALZENNA occurred in 32% of patients. Serious adverse reactions reported in >2% of patients included anemia (6%) and pyrexia (2%). Fatal adverse reactions occurred in 1% of patients, including cerebral hemorrhage, liver disorder, veno-occlusive liver disease, and worsening neurological symptoms (1 patient each).

Permanent discontinuation due to adverse reactions occurred in 5% of TALZENNA patients. Dosing interruptions due to an adverse reaction of any grade occurred in 65% of patients receiving TALZENNA; dose reductions due to any cause occurred in 53% of TALZENNA patients.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were hemoglobin decreased, neutrophils decreased, lymphocytes decreased, platelets decreased, fatigue, glucose increased, aspartate aminotransferase increased, alkaline phosphatase increased, alanine aminotransferase increased, calcium decreased, nausea, headache, vomiting, alopecia, diarrhea, and decreased appetite.

Table 3 and Table 4 summarize the most common adverse reactions and laboratory abnormalities, respectively, in patients treated with TALZENNA or chemotherapy in the EMBRACA study.

Table 3. Adverse Reactions[a] (≥20%) in Patients Receiving TALZENNA in EMBRACA

	TALZENNA N=286 (%)			Chemotherapy N=126 (%)		
Adverse Reactions	**Grades 1-4**	**Grade 3**	**Grade 4**	**Grades 1-4**	**Grade 3**	**Grade 4**
General Disorders and Administration Site Conditions						
Fatigue[b]	62	3	0	50	5	0
Gastrointestinal Disorders						
Nausea	49	0.3	0	47	2	0
Vomiting	25	2	0	23	2	0
Diarrhea	22	1	0	26	6	0
Nervous System Disorders						
Headache	33	2	0	22	1	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	25	0	0	28	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	21	0.3	0	22	1	0

Abbreviation: N=number of patients.

a. Graded according to NCI CTCAE 4.03.

b. Includes fatigue and asthenia.

Clinically relevant adverse reactions in <20% of patients who received TALZENNA included abdominal pain (19%), dizziness (17%), dysgeusia (10%), dyspepsia (10%), stomatitis (8%), and febrile neutropenia (0.3%).

Table 4. Select Laboratory Abnormalities (≥25%) of Patients in EMBRACA

	TALZENNA N[a]=286 (%)			Chemotherapy N[a]=126 (%)		
Parameter	**Grades 1-4**	**Grade 3**	**Grade 4**	**Grades 1-4**	**Grade 3**	**Grade 4**
Hemoglobin decreased	90	39	0	77	6	0
Neutrophils decreased	68	17	3	70	21	17
Lymphocytes decreased	76	17	0.7	53	8	0.8
Platelets decreased	55	11	4	29	2	0
Glucose increased[b]	54	2	0	51	2	0
Aspartate aminotransferase Increased	37	2	0	48	3	0
Alkaline phosphatase increased	36	2	0	34	2	0
Alanine aminotransferase increased	33	1	0	37	2	0
Calcium decreased	28	1	0	16	0	0

Abbreviation: N=number of patients.

a. This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

b. This number represents non-fasting glucose.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on TALZENNA

Effect of P-gp Inhibitors

Breast Cancer

Avoid coadministration of TALZENNA with the following P-gp inhibitors: itraconazole, amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil. If coadministration of TALZENNA with these P-gp inhibitors cannot be avoided, reduce the dose of TALZENNA *[see Dosage and Administration (2.5)]*. When the P-gp inhibitor is discontinued, increase the dose of TALZENNA *[see Dosage and Administration (2.5)]*.

Coadministration of TALZENNA with these P-gp inhibitors increased talazoparib concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions.

Monitor for increased adverse reactions and modify the dosage as recommended for adverse reactions when TALZENNA is coadministered with other P-gp inhibitors *[see Dosage and Administration (2.3)]*.

Effect of Breast Cancer Resistance Protein (BCRP) Inhibitors
Monitor patients for increased adverse reactions and modify the dosage as recommended for adverse reactions when TALZENNA is coadministered with a BCRP inhibitor *[see Dosage and Administration (2.3)]*.

Coadministration of TALZENNA with BCRP inhibitors may increase talazoparib exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, TALZENNA can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on TALZENNA use in pregnant women to inform a drug-associated risk. In an animal reproduction study, the administration of talazoparib to pregnant rats during the period of organogenesis caused fetal malformations and structural skeletal variations and embryo-fetal death at maternal exposures that were 0.24 times the AUC in patients receiving the recommended dose of 1 mg daily *(see Data)*. Apprise pregnant women and females of reproductive potential of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data
Animal Data
In an embryo-fetal development toxicity study, pregnant rats received oral doses of 0.015, 0.05, and 0.15 mg/kg/day talazoparib during the period of organogenesis. Talazoparib caused embryo-fetal death at doses ≥0.015 mg/kg/day (approximately 0.24 times the AUC in patients at the recommended dose of 1 mg daily). A dose of 0.015 mg/kg/day caused decreased fetal body weights and an increased incidence of fetal malformations (depressed eye bulge, small eye, split sternebra, and fused cervical vertebral arch) and structural variations including misshapen or incomplete ossification of the sternebra, skull, rib, and vertebra.

8.2 Lactation

Risk Summary
There are no data on the presence of talazoparib in human milk, the effects of the drug on milk production, or the effects of the drug on the breastfed child. Because of the potential for serious adverse reactions in a breastfed child from talazoparib, advise lactating women not to breastfeed during treatment with TALZENNA and for 1 month after the last dose.

8.3 Females and Males of Reproductive Potential

TALZENNA can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TALZENNA treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of TALZENNA.

Males

Based on genotoxicity and animal reproduction studies, advise male patients with female partners of reproductive potential and pregnant partners to use effective contraception during treatment with TALZENNA and for 4 months following the last dose *[see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)]*.

Infertility

Males

Based on animal studies, TALZENNA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.5 Geriatric Use

In clinical trials of TALZENNA enrolling 494 patients with advanced solid tumors who received TALZENNA 1 mg daily as a single agent, 85 (17%) patients were ≥65 years of age, and this included 19 (4%) patients who were ≥75 years old. There were 5 patients ≥85 years old. No overall differences in safety or effectiveness of TALZENNA were observed between these patients and younger patients.

8.6 Hepatic Impairment

TALZENNA has not been studied in patients with moderate hepatic impairment (total bilirubin >1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST). No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤1 × ULN and AST > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST) *[see Clinical Pharmacology (12.3)]*.

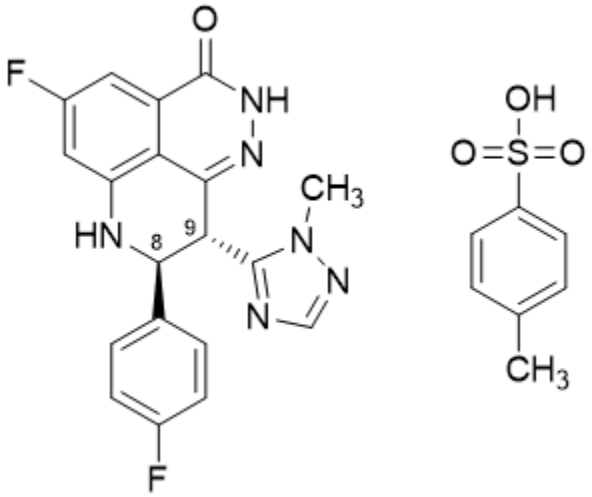
8.7 Renal Impairment

Reduce the recommended dosage of TALZENNA in patients with moderate (CLcr 30 – 59 mL/min) and severe (CLcr 15 – 29 mL/min) renal impairment *[see Dosage and Administration (2.4)]*. Monitor patients with severe renal impairment for increased adverse reactions and modify the dosage as recommended for adverse reactions *[see Dosage and Administration (2.4)]*.

No dose adjustment is recommended for patients with mild renal impairment (CLcr 60 – 89 mL/min). TALZENNA has not been studied in patients requiring hemodialysis.

11 DESCRIPTION

Talazoparib is an inhibitor of mammalian polyadenosine 5'-diphosphoribose (ADP-ribose) polymerase (PARP) enzymes. The chemical name of talazoparib tosylate is (8*S*,9*R*)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3*H*-pyrido[4,3,2-*de*]phthalazin-3-one 4-methylbenzenesulfonate (1:1). The chemical formula of talazoparib tosylate is $C_{26}H_{22}F_2N_6O_4S$, and the relative molecular mass is 552.56 Daltons. The chemical structure of talazoparib tosylate is shown below:



- Talazoparib tosylate is a white to yellow solid. TALZENNA capsules for oral use are available as a 0.25 mg hard hypromellose (HPMC) capsule that contains 0.363 mg talazoparib tosylate equivalent to 0.25 mg talazoparib free base or as a 1 mg HPMC capsule that contains 1.453 mg talazoparib tosylate equivalent to 1 mg talazoparib free base.

Inactive ingredients: Blend composition contains silicified microcrystalline cellulose (Prosolv® 90), silicified microcrystalline cellulose (Prosolv® 50). Talzenna 0.25 mg white/ivory opaque capsule shells contains Hypromellose, titanium dioxide, yellow iron oxide. Talzenna 1 mg white/light red opaque capsule shells contains Hypromellose, titanium dioxide, red iron oxide, yellow iron oxide; and the printing ink contains shellac, black iron oxide, propylene glycol, ammonium hydroxide and potassium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Talazoparib is an inhibitor of PARP enzymes, including PARP1 and PARP2, which play a role in DNA repair. *In vitro* studies with cancer cell lines that harbored defects in DNA repair genes, including *BRCA1* and *BRCA2*, have shown that talazoparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, decreased cell proliferation, and apoptosis. Talazoparib anti-tumor activity was observed in patient-derived xenograft breast cancer models bearing mutated *BRCA1* or mutated *BRCA2* or wild type *BRCA1* and *BRCA2*.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of TALZENNA have not been fully characterized.

Cardiac Electrophysiology

At a dose of 1 mg (the recommended dosage for treatment of breast cancer), TALZENNA had no large QTc prolongation (i.e., >20 ms).

12.3 Pharmacokinetics

After administration of TALZENNA 1 mg orally once daily as a single agent (the recommended dosage for breast cancer), the mean [% coefficient of variation (CV%)] AUC and maximum observed plasma concentration (C_{max}) of talazoparib at steady-state was 208 (37%) ng.hr/mL and 16.4 (32%) ng/mL, respectively. The mean (CV%) steady-state C_{trough} was 3.53 (61%) ng/mL.

The pharmacokinetics (PK) of talazoparib is linear from 0.025 mg to 2 mg (2 times the recommended dose for breast cancer). The median accumulation ratio of talazoparib following 1 mg orally once daily is 2.3 to 5.2. Talazoparib plasma concentrations reached steady-state within 2 to 3 weeks when administered as a single agent.

Absorption

The median time to C_{max} (T_{max}) was generally between 1 to 2 hours after dosing.

Food Effect

Following a single TALZENNA 0.5 mg dose with high-fat, high-calorie food (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), the mean C_{max} was decreased by 46%, the median T_{max} was delayed from 1 to 4 hours, and AUC was not affected.

Distribution

The mean apparent volume of distribution of talazoparib is 420 L. *In vitro*, protein binding of talazoparib is 74% and is independent of talazoparib concentration.

Elimination

The mean terminal plasma half-life (±standard deviation) is 90 (±58) hours and the mean apparent oral clearance (inter-subject variability) is 6.45 L/h (31%).

Metabolism

Talazoparib undergoes minimal hepatic metabolism. The identified metabolic pathways include mono-oxidation, dehydrogenation, cysteine conjugation of mono-desfluoro-talazoparib, and glucuronide conjugation.

Excretion

Excretion of talazoparib in urine was the major route of elimination. Approximately 68.7% (54.6% unchanged) of the total administered radiolabeled dose of talazoparib was recovered in urine, and 19.7% (13.6% unchanged) was recovered in feces.

Specific Populations

Age (18 to 88 years), sex, race (361 White, 41 Asian, 16 Black, 9 Others, and 63 Not Reported), and body weight (36 to 162 kg) had no clinically significant effect on the PK of talazoparib.

Patients with Renal Impairment

Mild (eGFR 60 – 89 mL/min/1.73 m^2) renal impairment had no clinically significant effect on talazoparib pharmacokinetics. Talazoparib steady-state total exposure (AUC) increased by 43% in subjects with moderate (eGFR 30 – 59 mL/min/1.73 m^2) renal impairment and 163% in patients with severe (eGFR 15 – 29 mL/min/1.73 m^2) renal impairment relative to subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2). Talazoparib steady-state peak concentration (C_{max}) increased by 32% in subjects with moderate renal impairment and 89% in subjects with severe renal impairment, relative to subjects with normal renal function.. The PK of talazoparib has not been studied in patients requiring hemodialysis. There was no evidence of a relationship between the protein binding of talazoparib and renal function.

Patients with Hepatic Impairment

Mild hepatic impairment (total bilirubin ≤1.0 × ULN and AST > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST) had no effect on the PK of talazoparib. The PK of talazoparib have not been studied in patients with moderate (total bilirubin >1.5 to 3.0 × ULN and any AST) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST).

Drug Interaction Studies

Clinical Studies

Effect of P-gp Inhibitors: Coadministration of a P-gp inhibitor (itraconazole) with a single 0.5 mg dose of TALZENNA increased talazoparib AUC and C_{max} by approximately 56% and 40%, respectively. Coadministration with the following other P-gp inhibitors: amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil increased talazoparib exposure by 45%.

Coadministration with other P-gp inhibitors (including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin) had no clinically significant effect on talazoparib pharmacokinetics.

Effect of P-gp Inducers: Coadministration of a P-gp inducer (rifampin) with a single 1 mg dose of TALZENNA increased talazoparib C_{max} by 37% with no effect on talazoparib AUC.

Effect of Acid-Reducing Agents: Coadministration of acid-reducing agents including proton pump inhibitors (PPI), histamine receptor 2 antagonists (H_2RA), or other acid-reducing agents has no effect on the absorption of talazoparib.

In Vitro Studies

Transporters: Talazoparib is a substrate of P-gp and BCRP transporters, but not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, BSEP, MATE1, or MATE2-K.

Talazoparib is not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, BSEP, MATE1, or MATE2-K.

CYP Enzymes: Talazoparib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.

Talazoparib is not an inducer of CYP1A2, CYP2B6, or CYP3A4.

UGT: Talazoparib is not an inhibitor of UGT isoforms (1A1, 1A4, 1A6, 1A9, 2B7, and 2B15).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with talazoparib.

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. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of talazoparib, indicating the potential for genotoxicity in humans. Talazoparib was not mutagenic in a bacterial reverse mutation (Ames) test.

Fertility studies in animals have not been conducted with talazoparib. In repeat-dose toxicity studies up to 3-months duration, talazoparib-related findings in the testis and epididymis at doses ≥0.04 mg/kg/day in rats and ≥0.01 mg/kg/day in dogs included decreased organ weights, luminal cellular debris, reduced sperm, and degeneration/atrophy. These doses in rats and dogs resulted in approximately 1.0 times and 0.2 times, respectively, the exposure (AUC) in humans at the recommended dose of 1 mg daily. Follicular atresia of the ovary was observed in rats at doses ≥1 mg/kg/day talazoparib, approximately 9.5 times the AUC in patients at the recommended dose of 1 mg daily.

14 CLINICAL STUDIES

14.1 Deleterious or Suspected Deleterious Germline *BRCA*-mutated HER2-negative Locally Advanced or Metastatic Breast Cancer

EMBRACA (NCT01945775) was an open-label study in which patients (N=431) with g*BRCA*m HER2-negative locally advanced or metastatic breast cancer were randomized 2:1 to receive TALZENNA 1 mg or healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. Randomization was stratified by prior lines 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 (CNS) metastasis (yes versus no).

Patients 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 treatment setting. First-line treatment for advanced or metastatic disease with no prior adjuvant chemotherapy was allowed if the investigator determined that 1 of the 4 chemotherapy choices in the control arm would be an appropriate treatment option for the patient. 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 randomized in the EMBRACA study, 408 (95%) were centrally confirmed to have a deleterious or suspected deleterious g*BRCA*m 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.

The median age of patients treated with TALZENNA was 46 years (range 28 to 84) and 51 years (range 24 to 89) among patients treated with chemotherapy. Among all randomized patients, 1% versus 2% were males, 67% versus 75% were White; 11% versus 11% were Asian, and 4% versus 1% were Black or African American in the TALZENNA and chemotherapy arms, respectively. Almost all patients (98%) in both arms had an

Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Approximately 56% of patients had estrogen receptor-positive and/or progesterone receptor-positive disease; 44% of patients had triple-negative disease, and the proportions were balanced across both treatment arms. Fifteen percent (15%) of patients in the TALZENNA arm and 14% of patients in the chemotherapy arm had a history of CNS metastases. Ninety-one percent (91%) of patients in the TALZENNA arm had received prior taxane therapy, and 85% had received prior anthracycline therapy in any setting. Sixteen percent (16%) of patients in the TALZENNA arm and 21% of patients in the chemotherapy arm had received prior platinum treatment in any setting. The median number of prior cytotoxic regimens for patients with advanced breast cancer was one; 38% received no prior cytotoxic regimens for advanced or metastatic disease, 37% received one, 20% received two, and 5% received three or more prior cytotoxic regimens.

The major efficacy outcome measure 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). A statistically significant improvement in PFS was demonstrated for TALZENNA compared to chemotherapy. A sensitivity analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results. Consistent PFS results were observed across patient subgroups defined by study stratification factors (prior lines of chemotherapy, TNBC status, and history of CNS metastases). Efficacy data from the EMBRACA study are summarized in Table 9, and the Kaplan-Meier curves for PFS are shown in Figure 1 and final overall survival (OS) in Figure 2.

Table 5. Efficacy Results – EMBRACA Study

	TALZENNA	**Chemotherapy**
PFS by BICR	N=287	N=144
Disease progression or deaths, n (%)	186 (65)	83 (58)
Median months (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard ratio (95% CI)[a]	0.54 (0.41, 0.71)	
p-value[b]	p<0.0001	
Patients with Measurable Disease by Investigator[c]	N=219	N=114
ORR, % (95% CI)[d]	50.2 (43.4, 57.0)	18.4 (11.8, 26.8)
Median[e] DOR months (95% CI)	6.4 (5.4, 9.5)	3.9 (3.0, 7.6)
OS	N=287	N=144
Deaths, n (%)	216 (75)	108 (75)
Median months (95% CI)	19.3 (16.6, 22.5)	19.5 (17.4, 22.4)
Hazard ratio (95% CI)[a]	0.85 (0.67, 1.07)	
p-value[b]	p=0.1693	

Abbreviations: BICR=blinded independent central review; CI=confidence interval; DOR=duration of response; ITT=intent-to-treat; N=number of patients; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

a. Hazard ratio is estimated from a Cox proportional hazards model 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 by history of central nervous system metastasis (yes versus no) and is relative to overall chemotherapy with <1 favoring talazoparib.

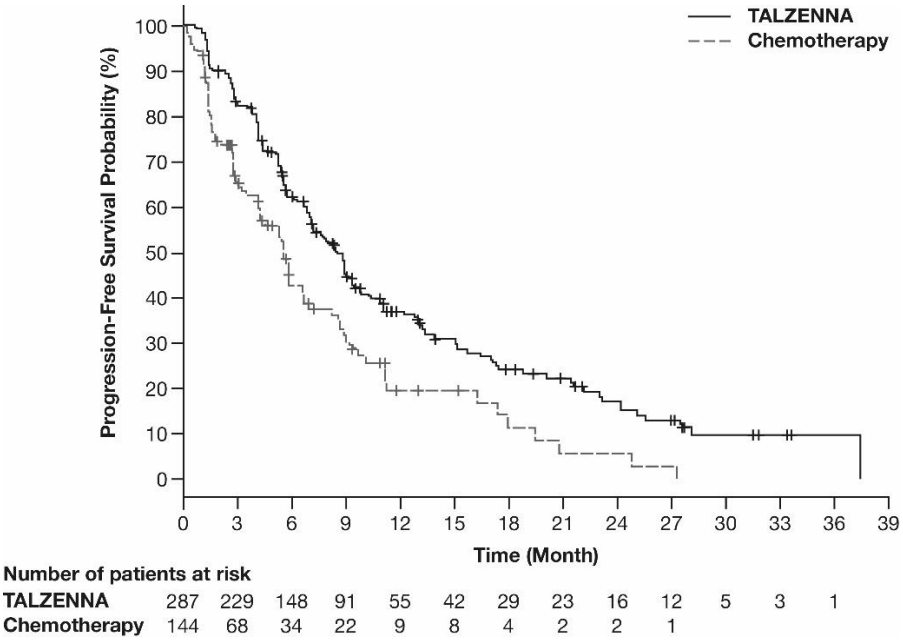
b. p-values (2-sided) from the log-rank test stratified by number of prior cytotoxic chemotherapy regimens, triple-negative status and history of central nervous system metastasis.

c. Conducted in ITT population with measurable disease at baseline.

d. Response rate based on confirmed responses.

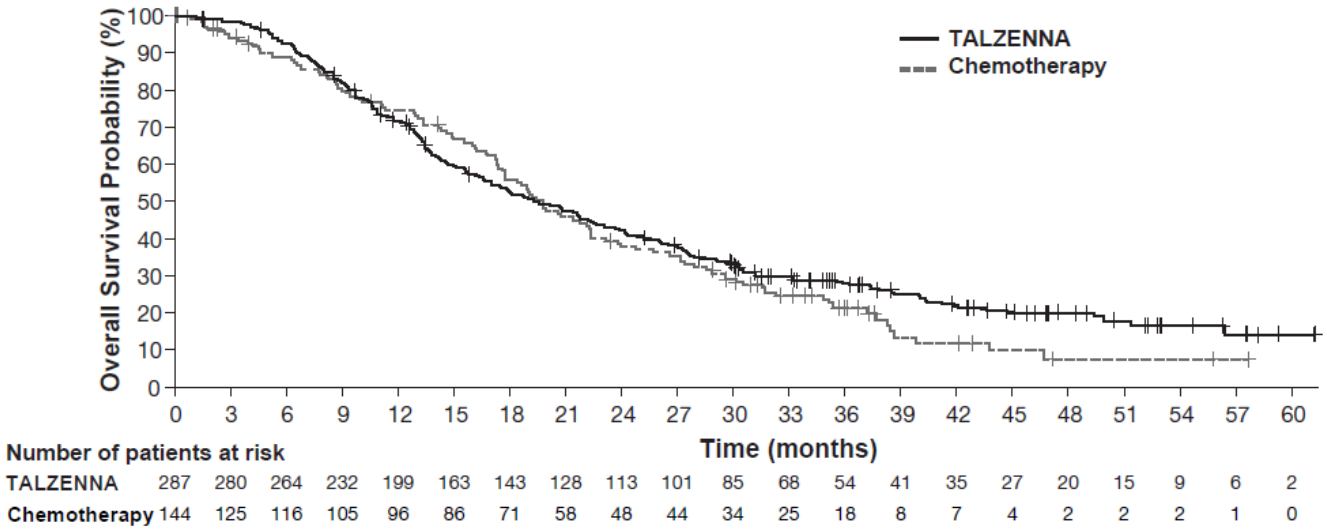
e. Median estimated from Kaplan-Meier probabilities.

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



Abbreviation: PFS=progression-free survival.

Figure 2. Kaplan-Meier Curves of OS – EMBRACA Study (ITT Population)



Abbreviations: ITT=intent-to-treat; OS=overall survival.

16 HOW SUPPLIED/STORAGE AND HANDLING

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) 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) unit dose blister with an aluminum peel off foil lidding. Pack size: cartons of 30 × 1 capsules in unit dose blisters.

Not all pack types and sizes may be marketed.

Storage
This medicinal product does not require any special storage conditions.
It is recommended to store in room temperature.

Shelf life
The expiry date of the product is indicated on the packaging materials.

Marketing Authorization Holder
Pfizer Pharmaceuticals Israel Ltd. 9 Shenkar St., Herzliya Pituach 46725

License Number
Talzenna 0.25 mg: 164-07-36019
Talzenna 1 mg: 164-08-36033

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