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 (*gBRCAm*) 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 (8.6), 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) have been reported in patients who received TALZENNA. Overall, MDS/AML has been reported in <1% (3 out of 787, 0.4%) of solid tumor patients treated with TALZENNA in clinical studies. The duration 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 complete blood counts for cytopenia at baseline and monthly thereafter. For prolonged hematological toxicities, interrupt TALZENNA and monitor blood counts weekly until recovery. If the levels have not recovered after 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, leukopenia/neutropenia, and/or thrombocytopenia, have been reported in patients treated with TALZENNA *[see Adverse Reactions (6)]*. Grade ≥3 anemia, neutropenia, and thrombocytopenia were reported, respectively, in 39%, 21%, and 15% of patients receiving TALZENNA. Discontinuation due to anemia, neutropenia, and thrombocytopenia occurred, respectively, in 0.7%, 0.3%, and 0.3% of patients.

Monitor complete blood count for cytopenia at baseline and monthly thereafter. Do not start TALZENNA until patients have adequately recovered from hematological toxicity caused by previous therapy. If this occurs, dose modifications (dosing interruption with or without dose reduction) are recommended *[see Dosing Modifications (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 at least 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 at least 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.

Treatment of *gBRCAm* HER2-negative Locally Advanced or Metastatic Breast Cancer

EMBRACA
The safety of TALZENNA as monotherapy was evaluated in gBRCAm 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. 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. Dosing interruptions due to an adverse reaction of any grade occurred in 65% of patients receiving TALZENNA and 50% of those receiving chemotherapy; dose reductions due to any cause occurred in 53% of TALZENNA patients and 40% of chemotherapy patients. Permanent discontinuation due to adverse reactions occurred in 5% of TALZENNA patients and 6% chemotherapy patients.

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] (in ≥20% of Patients Receiving TALZENNA) in EMBRACA

Adverse Reactions	TALZENNA N=286 (%)			Chemotherapy N=126 (%)		
	Grades 1-4	Grade 3	Grade 4	Grades 1-4	Grade 3	Grade 4
Blood and lymphatic system disorders						
Anemia[b]	53	38	1	18	4	1
Neutropenia[c]	35	18	3	43	20	16
Thrombocytopenia[d]	27	11	4	7	2	0
Metabolism and nutrition disorders						
Decreased appetite	21	<1	0	22	1	0
Nervous system disorders						
Headache	33	2	0	22	1	0
Gastrointestinal disorders						
Nausea	49	<1	0	47	2	0
Vomiting	25	2	0	23	2	0
Diarrhea	22	1	0	26	6	0
Skin and subcutaneous tissue disorders						
Alopecia[e]	25	0	0	28	0	0
General disorders and administration site conditions						
Fatigue[f]	62	3	0	50	5	0

Abbreviations: AR=adverse reaction; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; N=number of patients.

a. Graded according to NCI CTCAE 4.03.
b. Includes anemia, hematocrit decreased, hemoglobin decreased, and red blood cell count decreased.
c. Includes febrile neutropenia, neutropenia and neutrophil count decreased.
d. Includes thrombocytopenia and platelet count decreased.
e. For TALZENNA, Grade 1 in 23%, and Grade 2 in 2%. For the chemotherapy arm, Grade 1 in 20%, and Grade 2 in 8%.
f. Includes fatigue and asthenia.

The following adverse reactions have been identified in <20% of the 286 patients receiving TALZENNA, and thus were not included in Table 3: abdominal pain (19%), dizziness (17%), leukopenia (17%), dysgeusia (10%), dyspepsia (10%), stomatitis (8%), and lymphopenia (7%).

Table 4 Laboratory Abnormalities Reported in ≥25% of Patients in EMBRACA

	EMBRACA Study					
	TALZENNA N[a]=286 (%)			Chemotherapy N[a]=126 (%)		
Parameter	**Grades 1-4**	**Grade 3**	**Grade 4**	**Grades 1-4**	**Grade 3**	**Grade 4**
Decrease in hemoglobin	90	39	0	77	6	0
Decrease in leukocytes	84	14	0.3	73	22	2
Decrease in neutrophils	68	17	3	70	21	17
Decrease in lymphocytes	76	17	0.7	53	8	0.8
Decrease in platelets	55	11	4	29	2	0
Increase in glucose[b]	54	2	0	51	2	0
Increase in aspartate aminotransferase	37	2	0	48	3	0
Increase in alkaline phosphatase	36	2	0	34	2	0
Increase in alanine aminotransferase	33	1	0	37	2	0
Decrease in calcium	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

Coadministration with P-gp inhibitors may increase talazoparib exposure.

In patients with advanced solid tumors, coadministration of a P-gp inhibitor (itraconazole) increased talazoparib plasma exposure by 56%. In the clinical studies, coadministration with P-gp inhibitors including amiodarone,

carvedilol, clarithromycin, itraconazole, and verapamil resulted in an approximate 45% increase in talazoparib exposure and an increase in the rate of TALZENNA dose reduction. If coadministration of TALZENNA with these P-gp inhibitors cannot be avoided, reduce the TALZENNA dose *[see Dosage and Administration (2.5)]*. When the P-gp inhibitor is discontinued, increase the TALZENNA dose (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the P-gp inhibitor *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

When coadministering TALZENNA with P-gp inhibitors not listed above, monitor patients for potential increased adverse reactions *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

Effect of BCRP inhibitors

Coadministration with BCRP inhibitors may increase talazoparib exposure. If coadministration cannot be avoided, monitor patients for potential increased adverse reactions when coadministering *[see Clinical Pharmacology (12.3)]*.

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). 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 at least 1 month after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

A pregnancy test is recommended for females of reproductive potential prior to initiating TALZENNA treatment.

Contraception

Females
TALZENNA can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for at least 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 at least 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 monotherapy, 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, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Patients with moderate or severe renal impairment have a higher exposure to TALZENNA than patients with normal renal function. Reduce the recommended dose of TALZENNA in patients with moderate (CLcr 30 – 59 mL/min) and severe (CLcr 15 – 29 mL/min) renal impairment. Monitor patients with severe renal impairment for potential increased adverse reactions and adjust dosing accordingly *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*. No dose adjustment is required for patients with mild renal impairment (CLcr 60 – 89 mL/min). TALZENNA has not been studied in patients requiring hemodialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

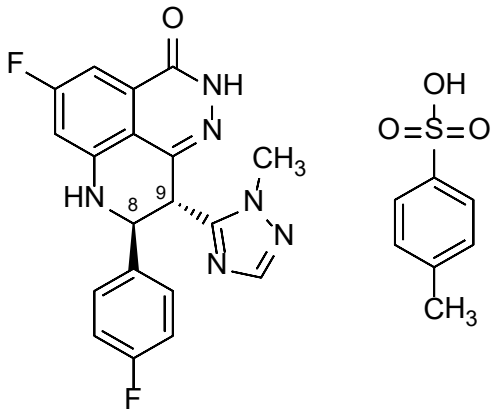
TALZENNA has not been studied in patients with moderate hepatic impairment (total bilirubin >1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST). No dose adjustment is required for patients with mild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

10 OVERDOSAGE

There is no specific treatment in the event of TALZENNA overdose, and symptoms of overdose have not been established. In the event of overdose, discontinue treatment with TALZENNA, consider gastric decontamination, follow general supportive measures, and treat symptomatically.

11 DESCRIPTION

Talazoparib is an inhibitor of mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme. 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 poly (ADP-ribose) polymerase (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 BRCA 1 and BRCA 2, 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 human patient-derived xenograft breast cancer tumor models bearing mutated BRCA 1 or mutated BRCA 2 or wild-type BRCA 1 and BRCA 2.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of talazoparib on cardiac repolarization was evaluated in 37 patients with advanced solid tumors. Talazoparib had no large QTc prolongation (i.e., >20 ms) at the recommended dose.

12.3 Pharmacokinetics

After oral administration of 1 mg TALZENNA once daily in patients, the recommended dose, the geometric mean [% coefficient of variation (CV%)] of 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 pharmacokinetics (PK) of talazoparib is linear from 0.025 mg to 2 mg (2 times the recommended dose). 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 plasma concentrations reached steady-state within 2 to 3 weeks.

Absorption

Following oral administration of talazoparib, the median time to C_{max} (T_{max}) was generally between 1 to 2 hours after dosing.

Food Effect
Following a single oral dose of 0.5 mg TALZENNA 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} of talazoparib was decreased by 46%, the median T_{max} was delayed from 1 to 4 hours, and AUC_{inf} 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) of talazoparib is 90 (±58) hours, and the mean apparent oral clearance (inter-subject variability) is 6.45 L/h (31.1%) in cancer patients.

Metabolism

Talazoparib undergoes minimal hepatic metabolism. The identified metabolic pathways of talazoparib in humans 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 radioactive dose [^{14}C]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 relevant effect on the PK of talazoparib.

Patients with Renal Impairment

Talazoparib steady-state total exposure (AUC_{0-24}) increased by 12%, 43%, and 163% in patients with mild (eGFR 60 – 89 mL/min/1.73 m^2), moderate (eGFR 30 – 59 mL/min/1.73 m^2), and severe (eGFR 15 – 29 mL/min/1.73 m^2) renal impairment, respectively, relative to patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2). Talazoparib steady-state peak concentration (C_{max}) increased by 11%, 32%, and 89% in patients with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function. 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

Effect of Other Drugs on Talazoparib

Effect of P-gp inhibitors: In patients with advanced solid tumors, coadministration of a P-gp inhibitor (multiple 100 mg twice-daily doses of itraconazole) with a single 0.5 mg talazoparib dose increased talazoparib AUC_{inf} and C_{max} by approximately 56% and 40%, respectively. Population PK analysis showed that coadministration with P-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil in clinical studies increased talazoparib exposure by 45% *[see Dosage and Administration (2.5), Drug Interactions (7.1)]*.

Coadministration with P-gp inhibitors including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin in clinical studies increased talazoparib exposure by 8% *[see Dosage and Administration (2.5), Drug Interactions (7)]*.

Effect of P-gp inducers: In patients with advanced solid tumors, coadministration of a P-gp inducer (multiple 600 mg once-daily doses of rifampin) with a single 1 mg talazoparib dose increased talazoparib C_{max} by 37% with no effect on talazoparib exposure.

Effect of BCRP inhibitors: The effect of BCRP inhibitors on PK of talazoparib has not been studied. Coadministration with BCRP inhibitors may increase talazoparib exposure *[see Drug Interactions (7)]*.

Effect of acid-reducing agents on talazoparib: 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
Talazoparib is a substrate of P-gp and BCRP transporters.

Talazoparib is not a substrate of 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.

Talazoparib is not an inhibitor of cytochrome (CYP)1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5, or inducer of CYP1A2, CYP2B6, or CYP3A4.

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

Talazoparib is not an inhibitor of uridine-diphosphate glucuronosyltransferase (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. 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.

14 CLINICAL STUDIES

EMBRACA Study (NCT01945775)

Deleterious or Suspected Deleterious Germline BRCA-mutated *(gBRCAm)* HER2-negative Locally Advanced

or Metastatic Breast Cancer

EMBRACA (NCT01945775) was an open-label study in which patients (N=431) with gBRCAm 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 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.

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 with 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 5, and the Kaplan-Meier curves for PFS are shown in Figure 1 and final overall survival (OS) in Figure 2.

Table 5. Summary of 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; 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 was relative to overall chemotherapy with <1 favoring talazoparib.

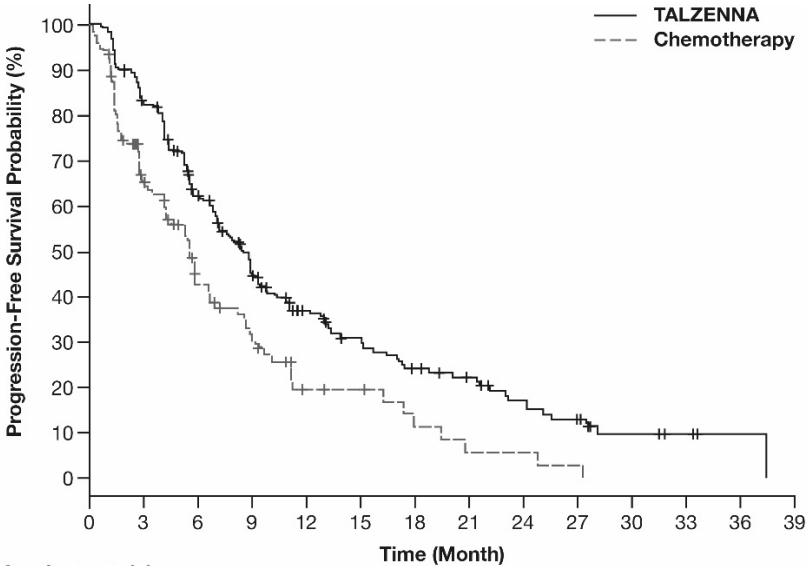
[b] P-values (2-sided) from the log-rank test stratified by number of prior cytotoxic chemotherapy regimens, triple negative status and history of central nervous system metastasis.

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

[d] Response rate based on confirmed responses.

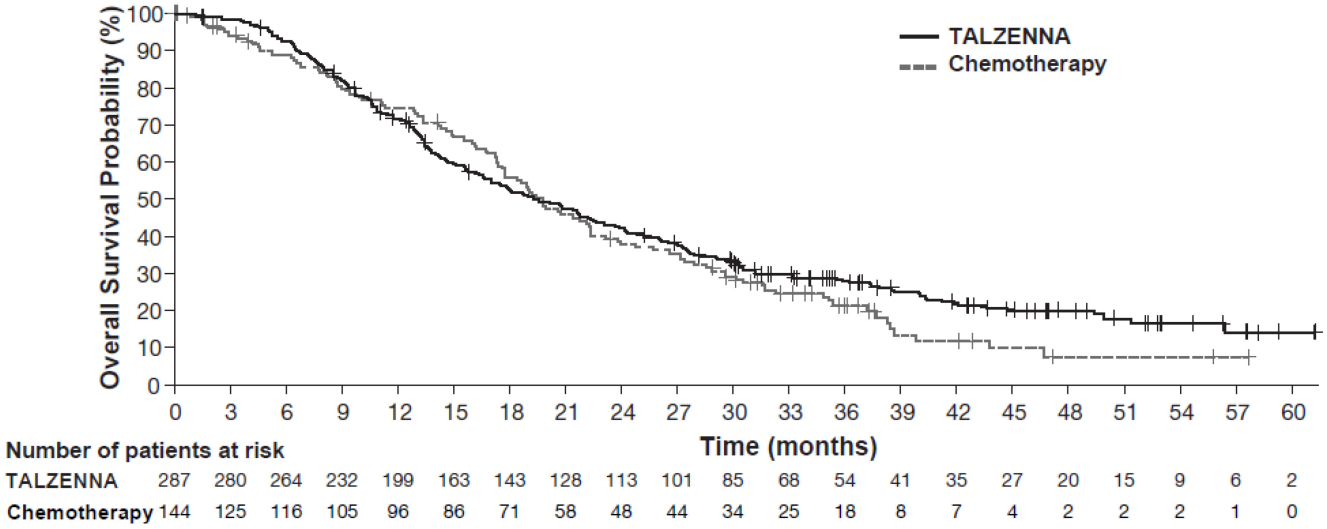
[e] Median estimated from Kaplan-Meier probabilities.

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)



Abbreviation: 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
Do not store above 30°C

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

After first opening the bottle can be used for up to six months and no later than the expiry date 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

Revised in 11/2021 according to MOH guidelines.