▼ This medicinal product is subject to additional monitoring **in Australia**. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

TALZENNA® (TALAZOPARIB)

1. NAME OF THE MEDICINE

Australian Approved Name (AAN): talazoparib, talazoparib tosilate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TALZENNA 0.25 mg strength
Each capsule contains 0.363 mg talazoparib tosilate equivalent to 0.25 mg talazoparib free base.

TALZENNA 1 mg strength
Each capsule contains 1.453 mg talazoparib tosilate equivalent to 1 mg talazoparib free base.

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

3. PHARMACEUTICAL FORM

Hard capsule

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TALZENNA is indicated for the treatment of patients with a deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA) mutation according to a validated diagnostic test, who have human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer.

4.2 Dose and method of administration

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

Detection of BRCA mutation

Detection of mutations in hereditary breast cancer-related BRCA1 and BRCA2 genes should be determined by an experienced laboratory using a validated test method (see Section 4.4 Special warnings and precautions for use - Diagnostic test selection).

Dosage and method of administration

The recommended dose of TALZENNA is 1 mg taken orally once daily, with or without food. The capsules should be swallowed whole and must not be opened or dissolved.

The 0.25 mg strength capsule is available for dose reduction.

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

Missed 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.

Dosage adjustment

To manage adverse reactions, consider interruption of treatment or dose reduction based on severity and clinical presentation. Recommended dose reductions are indicated in Table 1. Discontinue TALZENNA if more than three dose reductions are required.

Table 1. Dose Modification for Toxicities

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

Full blood counts should be obtained prior to starting TALZENNA therapy and monitored monthly and as clinically indicated (see Table 2 and Section 4.4 Special warnings and precautions for use).

Table 2. Dose Modification and Management

	Withhold TALZENNA until levels resolve to	**Resume TALZENNA**
Haemoglobin <80 g/L	≥90 g/L	Resume TALZENNA at a reduced dose
Platelet count <50 x 10^9/L	≥75 x 10^9/L	

Neutrophil count <1 x 10^9/L	≥1.5 x 10^9/L	
Non-haematologic adverse reaction Grade 3 or Grade 4	≤Grade 1	Consider resuming TALZENNA at a reduced dose or discontinue.

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

Strong inhibitors of P-gp may lead to increased talazoparib exposure. Concomitant use of strong P-gp inhibitors during treatment with talazoparib should be avoided. Coadministration should only be considered after careful evaluation of the potential benefits and risks. If coadministration with a strong P-gp inhibitor is unavoidable, the TALZENNA dose should be reduced to the next lower dose level (see Table 1). When the strong P-gp inhibitor is discontinued, the TALZENNA dose should be increased (after 3 to 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 Interactions with other medicines and other forms of interactions - P-gp inhibitors).

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤1 × upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST). TALZENNA has not been studied in patients with moderate (total bilirubin >1.5 to 3.0 × ULN and any AST) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST) (see Section 5.2 Pharmacokinetic properties - Hepatic impairment).

Renal impairment

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

Elderly population

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

4.3 Contraindications

Use of TALZENNA is contraindicated in patients with hypersensitivity to talazoparib tosilate or any of the excipients listed in Section 6.1 List of excipients.

4.4 Special warnings and precautions for use

Myelodysplastic syndrome/Acute Myeloid Leukaemia

Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in patients who received talazoparib. Overall, MDS/AML has been reported in 2 out of 584 (0.3%) solid tumour patients treated with talazoparib in clinical studies. Both patients had received previous platinum-containing chemotherapy and/or other DNA damaging agents including radiotherapy.

Do not start TALZENNA until patients have adequately recovered from haematological toxicity caused by previous chemotherapy. Monitor full blood counts for cytopenia at baseline and monthly thereafter. For prolonged haematological toxicities, interrupt TALZENNA and monitor blood counts weekly until recovery. If the levels have not recovered after 4 weeks, refer the patient to a haematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue talazoparib.

Myelosuppression

Myelosuppression, consisting of anaemia, leucopenia/neutropenia and/or thrombocytopenia, is very common in patients treated with talazoparib (see Section 4.8 Adverse effects).

Do not start talazoparib until patients have recovered from haematological toxicity caused by previous therapy (≤ Grade 1). Monitor clinically and check full blood counts for cytopenia at baseline and monthly thereafter. If haematological toxicity occurs, dose modification (interruption with or without reduction) is recommended (see Section 4.2 Dose and method of administration - Dosage adjustment). Provide supportive care, transfusion of blood/platelets and treatment with colony stimulating factors as appropriate.

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 total area under the concentration-time curve (AUC) in patients receiving the recommended human dose of 1 mg daily (see Section 5.3 Preclinical safety data – Reproductive toxicology).

Conduct a blood test for pregnancy prior to initiating TALZENNA treatment in any female of reproductive potential. Advise 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 Section 4.6 Fertility, pregnancy and lactation – Use in pregnancy).

Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential and pregnant partners to use effective contraception (even after vasectomy), during treatment with TALZENNA and for at least 4 months after the final dose (see Section 4.6 Fertility, pregnancy and lactation – Use in pregnancy and Section 5.3 Preclinical safety data).

Use in the elderly

No overall differences in safety or effectiveness of TALZENNA were observed between patients ≥65 years of age and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see Section 5.2 Pharmacokinetic properties - Elderly population). No dose adjustment is required in elderly patients (see Section 4.2 Dose and method of administration - Dosage adjustment – Elderly population).

Paediatric use

The safety and efficacy of TALZENNA in children and adolescents <18 years of age have not been established.

Effects on laboratory tests

See Section 4.8 Adverse effects (undesirable effects).

Diagnostic test selection

When assessing a patient for mutations in hereditary breast cancer-related BRCA1 and BRCA2 genes, it is important that a well-validated and robust methodology is chosen to minimise false negative or false positive determinations.

4.5 Interactions with other medicines and other forms of interactions

Talazoparib is a substrate for drug transporters P-gp and Breast Cancer Resistance Protein (BCRP) and is mainly eliminated by renal clearance as unchanged compound. Information on agents that may affect talazoparib plasma concentrations is provided below.

P-gp inhibitors

Coadministration with P-gp inhibitors may increase talazoparib exposure.

Data from a drug-drug interaction study in patients with advanced solid tumours indicated that coadministration of multiple daily doses of a P-gp inhibitor, itraconazole 100 mg twice daily, with a single 0.5 mg talazoparib dose increased talazoparib total exposure (AUC_{inf}) and peak concentration (C_{max}) by approximately 56% and 40%, respectively, relative to a single 0.5 mg talazoparib dose administered alone. A population pharmacokinetic (PK) analysis has also shown that concomitant use of strong P-gp inhibitors with TALZENNA increased talazoparib exposure by 44.7% relative to TALZENNA given alone.

If coadministration with a strong P-gp inhibitor, those that result in ≥2-fold increase in the exposure of an *in vivo* probe P-gp substrate, (including but not limited to amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valspodar and verapamil) is unavoidable, the TALZENNA dose should be reduced (see Section 4.2 Dose and method of administration - Dosage adjustment - Concomitant treatment with inhibitors of P-glycoprotein).

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

P-gp inducers

Data from a drug-drug interaction study in patients with advanced solid tumours indicated that coadministration of multiple daily doses of a P-gp inducer, rifampicin 600 mg, with a single 1 mg talazoparib dose increased talazoparib C_{max} by approximately 37% with no effect on talazoparib total exposure. No talazoparib dose adjustments are required with P-gp inducers.

Breast Cancer Resistance Protein (BCRP) inhibitors

The effect of BCRP inhibitors on the PK of talazoparib has not been studied. Coadministration with BCRP inhibitors may increase talazoparib exposure. Concomitant use of strong BCRP inhibitors (including but not limited to curcumin, ciclosporin and elacridar [GF120918]) should be avoided. If coadministration cannot be avoided, monitor patients for potential adverse reactions when coadministering.

Acid-reducing agents

A population PK analysis indicates that coadministration of acid-reducing agents including proton pump inhibitors (PPI), histamine receptor 2 antagonists (H2RA) or other acid-reducing agents had no significant impact on the absorption of talazoparib.

Administration with CYP substrates

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

Administration with substrates of transporters

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.

Administration with UGT substrates

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.

4.6 Fertility, pregnancy and lactation

Effects on fertility

There is no information on fertility in humans. Based on non-clinical findings in testes and ovary, male and female fertility may be compromised by treatment with TALZENNA (see Section 5.3 Preclinical safety data – Repeat-dose toxicity).

Use in pregnancy - Pregnancy Category D

There are no data from the use of TALZENNA in pregnant women. Based on findings from animal studies and its mechanism of action, TALZENNA can cause embryo-fetal harm when administered to a pregnant woman (see Section 5.3 Preclinical safety data – Reproductive toxicology).

TALZENNA is not recommended during pregnancy or for women of childbearing potential not using contraception (see Section 4.4 Special warnings and precautions for use – Embyro-fetal toxicity).

Use in lactation

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.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

Randomised Phase 3 study - EMBRACA

The safety of TALZENNA as monotherapy was evaluated in patients with a germline BRCA mutation and 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 (see Section 5.1 Pharmacodynamic properties – Clinical Trials) was a randomised, open-label, multi-centre study in which 412 patients received either TALZENNA 1 mg once daily (n=286) or a chemotherapy agent (capecitabine [n=55], eribulin [n=50], gemcitabine [n=12] or vinorelbine [n=9]) 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% of chemotherapy patients.

Table 3 and Table 4 summarise the most common adverse reactions and laboratory abnormalities, respectively, in patients treated with TALZENNA (n=286) or chemotherapy (n=126) in the EMBRACA study.

Table 3. Adverse Reactions (≥10%) in Patients Treated with TALZENNA or Chemotherapy in the EMBRACA Study

Adverse Reaction	TALZENNA (N=286)			Chemotherapy (N=126)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Blood and Lymphatic System Disorders						
Anaemia[a]	53	39	1	18	4	1
Neutropenia[b]	35	18	3	43	20	15
Thrombocytopenia[c]	27	11	4	7	2	0
Leucopenia[d]	17	6	<1	14	6	2
Metabolism and Nutrition Disorders						
Decreased appetite	21	<1	0	22	1	0
Nervous System Disorders						
Headache	33	2	N/A	22	1	N/A
Dizziness	17	<1	N/A	10	2	N/A
Dysgeusia	10	N/A	N/A	9	N/A	N/A
Gastrointestinal Disorders						
Nausea	49	<1	N/A	47	2	N/A
Vomiting	25	2	0	23	2	0
Diarrhoea	22	1	0	26	6	0
Abdominal pain[e]	19	1	N/A	21	3	N/A
Skin and Subcutaneous Tissue Disorders						
Alopecia[f]	25	N/A	N/A	28	N/A	N/A
General Disorders and Administration Site Conditions						
Fatigue[g]	62	3	0	50	5	0

Adverse event grades are evaluated based on NCI CTCAE (version 4.03). Patients with multiple events for a given preferred term are counted once only for each preferred term.

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; N=number of patients; N/A=not applicable.

* There were no Grade 5 adverse reactions.

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

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

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

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

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

f. For talazoparib, Grade 1 is 23% and Grade 2 is 2%. For chemotherapy, Grade 1 is 20% and Grade 2 is 8%.

g. Includes preferred terms of fatigue and asthenia.

The following adverse reactions have been identified in <10% of the 286 patients receiving TALZENNA and are not included in Table 3: lymphopenia (7.3%), dyspepsia (9.8%) and stomatitis (8.4%).

Table 4. Laboratory abnormalities reported in ≥25% of patients in EMBRACA

Parameter	TALZENNA N=286[a]			Chemotherapy N=126[a]		
	Grades 1-4 (%)	Grade 3 (%)	Grade 4 (%)	Grades 1-4 (%)	Grade 3 (%)	Grade 4 (%)
Decrease in haemoglobin	90	39	0	77	6	0
Decrease in leucocytes	84	14	<1	73	22	2
Decrease in neutrophils	68	17	3	70	21	17
Decrease in lymphocytes[e]	76	17	<1	53	8	<1
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

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 suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

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

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 harboured defects in DNA repair genes, including BRCA 1 and 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-tumour activity was observed in human patient-derived xenograft breast cancer tumour models that expressed mutated or wild-type BRCA 1 and 2.

Clinical trials

Randomised Phase 3 study - EMBRACA

EMBRACA was an open-label, randomised, multicentre study in which patients with a germline BRCA mutation who had HER2-negative locally advanced or metastatic breast cancer (n=431) were randomised 2:1 to receive TALZENNA 1 mg or healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, vinorelbine) until disease progression or unacceptable toxicity. Randomisation was stratified by prior lines of chemotherapy for metastatic disease (0 versus 1, 2 or 3), triple-negative disease status (triple-negative breast cancer [TNBC] versus non-TNBC) and history of central nervous system (CNS) metastasis (yes versus no).

Patients had 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. First-line treatment for advanced or metastatic disease with no prior adjuvant chemotherapy was allowed if the investigator determined that one of the 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 randomised in the EMBRACA study, 408 (95%) were centrally confirmed to have a deleterious or suspected deleterious germline BRCA mutation using a clinical trial assay, out of which 354 (82%) were confirmed using the BRACAnalysis® companion diagnostic test. A similar percentage of patients in both treatment arms had a BRCA1 versus BRCA2 mutation.

The median age of patients treated with TALZENNA was 45 years (range 27 to 84) and 50 years (range 24 to 88) among patients treated with chemotherapy. Of note, 63% versus 47% of patients were <50 years of age in the talazoparib and chemotherapy arms, respectively, 27% versus 47% were 50 to <65 years of age, and 9% versus 7% were ≥65 years of age. Among all randomised 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 talazoparib 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 hormone receptor (HR)-positive (either estrogen receptor [ER]-positive- or progesterone receptor [PR]-positive) disease; 44% of patients had triple-negative breast cancer (TNBC) and the proportions were balanced across 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 of patients in the talazoparib 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% had received no prior cytotoxic regimens for advanced or metastatic disease, 37% had received one, 20% had received two and 5% had received three or more prior cytotoxic regimens.

The primary efficacy endpoint was progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, as assessed by blinded independent central review (BICR). The secondary objectives were objective response rate (ORR), overall survival (OS), safety and PK. Exploratory objectives included duration of response (DOR).

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 (line of therapy, TNBC status and history of CNS metastases). The overall survival (OS) data were not mature at the time of the final PFS analysis (38% of patients had died). Efficacy data for EMBRACA are summarised in Table 5 and the Kaplan-Meier curve for PFS is shown in Figure 1.

Table 5. Summary of efficacy results – EMBRACA study

	Talazoparib	**Chemotherapy**
Progression-free survival by BICR	N=287	N=144
Events, number (%)	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	
Overall survival (interim analysis)[c]	N=287	N=144
Events, number (%)	108 (38%)	55 (38%)
Median (95% CI), months	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
Hazard ratio (95% CI)	0.76 (0.55, 1.06)	
2-sided p-value[b]	p=0.1053	
Patients with measurable disease by investigator assessment[d]	N=219	N=114
Objective response rate, % (95% CI)[e]	50.2 (43.4, 57.0)	18.4 (11.8, 26.8)
Median duration of response, months (95% CI)[f]	6.4 (5.4, 9.5)	3.9 (3.0, 7.6)

	Talazoparib	Chemotherapy

Abbreviations: BICR=blinded independent central review; CI=confidence interval.

a Estimated by Cox proportional hazards model, stratified by prior chemotherapy for metastatic disease (0 versus 1, 2 or 3 lines), by triple-negative disease status (triple-negative breast cancer [TNBC] versus non TNBC) and by history of central nervous system metastasis (yes versus no).

b. Stratified log-rank test (2-sided).

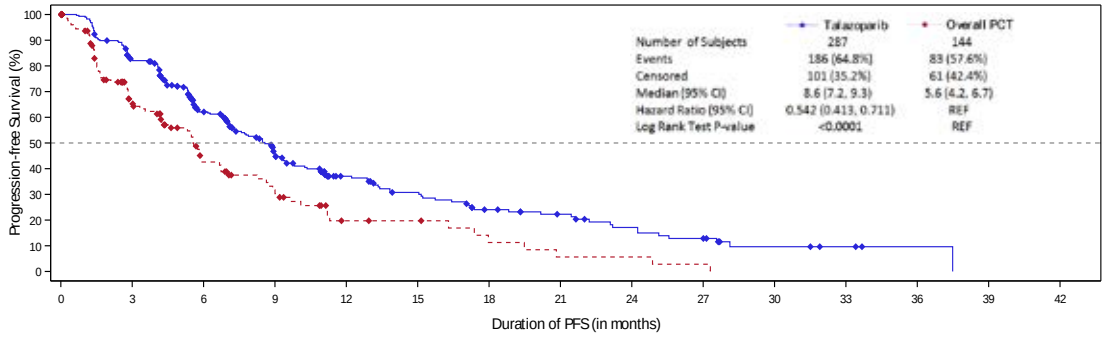
c. 51% of the projected final number of OS events occurred (163 of 321 deaths).

d. Conducted in the intent-to-treat population with measurable disease at baseline.

e. Based on confirmed responses. The complete response rate was 5% for talazoparib compared to 0% for the chemotherapy arm.

f. Estimated per Kaplan-Meier probabilities.

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



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

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

5.2 Pharmacokinetic properties

The pharmacokinetic profile of talazoparib is linear from0.025 mg to 2 mg (double the recommended daily dose). After oral administration of 1 mg talazoparib once daily in patients, the geometric mean (% coefficient of variation) area under the plasma concentration-time curve (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 median accumulation ratio of talazoparib following repeated oral administration of 1 mg once daily was in the range of 2.3 to 5.2, and talazoparib plasma concentrations reached steady-state within 2 to 3 weeks.

Absorption

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

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, and AUC_{inf} was not affected. Based on these results, TALZENNA can be administered with or without food.

Distribution

The population mean apparent volume of distribution (Vss/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.

Metabolism

Talazoparib undergoes minimal hepatic metabolism in humans. Following oral administration of a single 1 mg dose of [^{14}C]talazoparib, 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. The identified metabolic pathways of talazoparib in humans include: 1) mono-oxidation; 2) dehydrogenation; 3) cysteine conjugation of mono-desfluoro-talazoparib; and 4) glucuronide conjugation.

Excretion

The mean terminal plasma half-life of talazoparib was 89.8 hours and the population mean apparent oral clearance (CL/F) was 6.45 L/h in cancer patients. Excretion of talazoparib in urine was the major route of elimination (69% of the administered dose, 55% unchanged), and 20% was recovered in the faeces (14% unchanged).

Age, sex, race and body weight

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

Paediatric population

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

Elderly population

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

Hepatic impairment

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

Renal impairment

A population PK analysis that included 490 patients, where 132 patients had mild renal impairment (60 mL/min ≤ CrCL <90 mL/min), 33 patients had moderate renal impairment (30 mL/min ≤ CrCL <60 mL/min) and 1 patient had severe renal impairment (CrCL <30 mL/min), showed that talazoparib CL/F was decreased by 14% and 37% in patients with mild and moderate renal impairment, 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.

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.

5.3 Preclinical safety data

Genotoxicity

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. Talazoparib was not mutagenic in a bacterial reverse mutation (Ames) test.

Carcinogenicity

Carcinogenicity studies have not been conducted with talazoparib.

Repeat dose toxicity

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 exposures approximately 0.4 times and 0.3 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 5 times the AUC in patients at the recommended dose.

Reproductive toxicology

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 total 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Silicified microcrystalline cellulose

Capsule shell - White body (0.25 mg and 1 mg strengths)
Hypromellose
Titanium dioxide

Capsule shell - Ivory cap (0.25 mg strength)
Hypromellose
Titanium dioxide
Yellow iron oxide

Capsule shell – Light red cap (1 mg strength)
Hypromellose
Titanium dioxide
Red iron oxide
Yellow iron oxide

Printing Ink (TekPrint® SW-9008 Black)
Shellac
Propylene glycol
Ammonium hydroxide
Black iron oxide
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

TALZENNA 0.25 mg strength
High-density polyethylene (HDPE) bottles with child-resistant polypropylene closures containing 30 capsules.

Polyvinyl chloride/polyvinylidene chloride (PVC/PVdC) blister with an aluminium peel off foil lidding in cartons containing 30, 60 or 90 capsules.

TALZENNA 1 mg strength
HDPE bottles with child-resistant polypropylene closures containing 30 capsules.

PVC/PVdC blister with an aluminium peel off foil lidding in cartons containing 30 capsules.

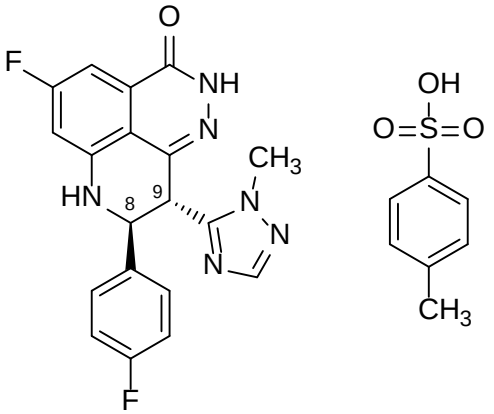
Not all presentations may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical Structure



CAS Number

Talazoparib tosilate: 1373431-65-2
Talazoparib: 1207456-01-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000
Toll Free number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

18 November 2019

10. DATE OF REVISION

Not Applicable

Summary table of changes

Not Applicable

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