PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**TALZENNA®**

Talazoparib Capsules

Capsules, 0.25 mg and 1 mg talazoparib (as talazoparib tosylate), Oral

Antineoplastic agent

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Quebec
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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	02/2022
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TALZENNA (talazoparib) is indicated as:

a monotherapy for the treatment of adult patients with a deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced (not amenable to curative radiation or surgery) or metastatic breast cancer, who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting, unless patients were inappropriate for these treatments.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of TALZENNA in children and adolescents <18 years of age have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): 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.

2 CONTRAINDICATIONS

TALZENNA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Treatment with TALZENNA should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products (See 1 INDICATIONS and 7 WARNINGS AND PRECAUTIONS)
- Myelodysplastic Syndrome/Acute Myeloid Leukemia has been reported in patients exposed to TALZENNA (See 7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis)
- TALZENNA can cause fetal harm when administered to a pregnant woman (see 7 WARNINGS AND PRECAUTIONS, Sexual Health, Reproduction)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

- Detection of a deleterious or suspected deleterious mutation(s) in hereditary breast cancer-related BRCA1 and BRCA2 genes should be determined by an experienced laboratory using a validated test method prior to treatment initiation.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of TALZENNA is 1 mg capsule taken orally once daily.

The 0.25 mg capsule is available for dose reduction.

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

Dose modifications
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.

Table 1. Dose Modification Recommendations for Toxicities

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 for the first 12 months of treatment and periodically thereafter and as clinically indicated (see 7 WARNINGS AND PRECAUTIONS).

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	≥50,000/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

During treatment with the 1 mg dose, switching from the 1 mg capsules to the 4 x 0.25 mg capsules is not recommended.

Concomitant treatment with inhibitors or inducers 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.

If coadministration with a strong P-gp inhibitor is unavoidable, the TALZENNA dose should be reduced to the next lower dose. When the strong P-gp inhibitor is discontinued, the TALZENNA dose should be increased (after 3 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 9.4 Drug-Drug Interactions).

Coadministration of rifampin, a strong P-gp inducer, had no significant impact on talazoparib exposure. No talazoparib dose adjustments are required when coadministered with rifampin. However, the effect of other P-gp inducers on talazoparib exposure has not been studied.

Concomitant treatment with inhibitors of Breast Cancer Resistance Protein (BCRP)
The effect of coadministration of BCRP inhibitors with TALZENNA has not been studied. Therefore, concomitant use of strong BCRP inhibitors during treatment with talazoparib should be avoided (see Section 9.4 Drug-Drug Interactions).

Special populations

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤1 × upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST), moderate hepatic impairment (total bilirubin >1.5 to 3.0 × ULN and any AST), or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST) (see Section 10.3 Pharmacokinetics, Special Populations and Conditions, 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. For patients with severe renal impairment (15 mL/min ≤ CrCL < 30 mL/min), the recommended dose of TALZENNA is 0.5 mg once daily. TALZENNA has not been studied in patients requiring hemodialysis (see Section 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Impairment).

Geriatric (≥65 years of age)
No dose adjustment is necessary in elderly (≥65 years of age) patients (see Section 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

Pediatric (<18 years)
The safety and efficacy of TALZENNA in children and adolescents <18 years of age have not been established. Health Canada has not authorized an indication for pediatric use.

4.4 Administration

The capsule(s) should be swallowed whole, and must not be opened, crushed, chewed or dissolved.

The capsules should be taken at approximately the same time every day and can be taken with or

without food.

4.5 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.

5 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3– Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule 0.25 mg: Each capsule contains 0.363 mg talazoparib tosylate equivalent to 0.25 mg talazoparib free base. 1 mg: Each capsule contains 1.453 mg talazoparib tosylate equivalent to 1 mg talazoparib free base.	Silicified microcrystalline cellulose 0.25 mg capsule shell: hypromellose, titanium dioxide, yellow iron oxide. 1 mg capsule shell: hypromellose, red iron oxide, titanium dioxide, yellow iron oxide. Printing ink: ammonium hydroxide, black iron oxide, potassium hydroxide, propylene glycol, shellac.

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

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

7 WARNINGS AND PRECAUTIONS

General
In order to receive TALZENNA, patients must have a deleterious or suspected deleterious germline mutation in a BRCA gene, as confirmed by an experienced laboratory using a validated BRCA assay. In the EMBRACA study, a majority of patient samples were sent to a centralized lab (Myriad Genetics) to confirm BRCA mutation status (BRACAnalysis).

Carcinogenesis and Mutagenesis
Secondary primary malignancies have been reported in patients that received TALZENNA.

Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML) have been reported in patients who received TALZENNA. Overall, MDS/AML has been reported in 2 out of 584 (0.3%) solid tumor patients treated with TALZENNA in clinical studies. The duration of TALZENNA treatment in these two patients prior to developing MDS/AML was 4 months and 24 months, respectively. Both patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Complete blood counts should be obtained at baseline and monitored monthly for signs of hematologic toxicity during treatment. If MDS/AML is confirmed, TALZENNA should be discontinued.

Driving and Operating Machinery

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery. 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 talazoparib should exercise caution when driving or operating machinery.

Hematologic
Myelosuppression consisting of anemia, neutropenia, and/or thrombocytopenia, have been reported in patients treated with TALZENNA. The frequency of Grade ≥ 3 for each event in patients who received TALZENNA at 1 mg daily in clinical studies was 35.2%, 17.4%, and 16.8%, respectively. The frequency of dose modifications for anemia, neutropenia, and thrombocytopenia was 33.0%, 15.8%, and 13.4%, respectively. Discontinuations due to these events were 0.6%, 0.2%, and 0.2%, respectively (see Section 8.1 Adverse Reaction Overview).

Do not start TALZENNA until patients have recovered from hematological toxicity caused by previous therapy (≤ Grade 1).

Precautions should be taken to monitor monthly for the first 12 months of treatment and periodically thereafter for hematology parameters (complete blood counts) and signs and symptoms associated with anemia, leukopenia/neutropenia, and/or thrombocytopenia in patients receiving TALZENNA. If such events occur, dose modifications (reduction or interruption) are recommended (see Section 8.1 Adverse Reaction Overview).

Supportive care with or without blood and/or platelet transfusions and/or administration of colony stimulating factors may be used as appropriate.

Sexual Health

Reproduction

Based on the mechanism of action and animal studies, talazoparib has demonstrated genotoxicity, reproductive organ toxicity, and embryofetal toxicity at subtherapeutic thresholds (see *Fertility*, section 7.1 Special Populations, Pregnant Women and Section 16 Non Clinical Toxicology). Therefore, talazoparib should not be given to pregnant patients or those who plan to become pregnant during treatment. Advise pregnant women of the potential risk to the fetus as TALZENNA can cause fetal harm when administered to a pregnant woman.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving TALZENNA. A highly effective method of contraception is required for female patients of childbearing potential during treatment with TALZENNA, and for at least 7 months after completing therapy.

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.

Male and female patients should not donate sperm or eggs during treatment and for 4 and 7 months after the last dose of TALZENNA, respectively.

Fertility

There is no information on fertility in patients. Based on non-clinical findings in the testes and ovary, male and female fertility may be compromised by treatment with TALZENNA (see Section 16 Non-Clinical Toxicology).

Monitoring and Laboratory Tests

BRCA Testing

Prior to treatment initiation, detection of a deleterious or suspected deleterious germline mutation(s) in a BRCA gene must be confirmed by an experienced laboratory using a validated test method.

Hematological testing

Complete blood counts should be obtained at baseline and monitored monthly for the first 12 months of treatment and periodically thereafter for signs of hematologic toxicity during treatment.

Pregnancy Testing

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

7.1 Special Populations

7.1.1 Pregnant Women

There are no clinical data from the use of TALZENNA in pregnant women. However, studies in animals have demonstrated genotoxicity and embryo-fetal toxicity including fetal malformations, decreased fetal weight, structural variations in bones and embryo-fetal death at sub therapeutic thresholds (see Section 16 Non-Clinical Toxicology). Therefore, TALZENNA can cause fetal harm when administered to a pregnant woman. TALZENNA should not be used during pregnancy or for women of childbearing

potential not using contraception.

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. If a female partner of a male patient receiving TALZENNA becomes pregnant, she should be apprised of the potential hazard to the fetus and the potential loss of the pregnancy.

7.1.2 Breast-feeding

It is unknown whether TALZENNA is excreted in human breast milk. A serious risk to newborns/infants cannot be excluded. Therefore, breastfeeding is not recommended during treatment with TALZENNA and for at least 1 month after the final dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of TALZENNA in children and adolescents <18 years of age have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety profile of TALZENNA is based on pooled data from 494 patients with a median duration of exposure of 5.4 months (range 0.03-61.1) who received TALZENNA at 1 mg daily in clinical studies for solid tumors, including 286 patients from a randomized Phase 3 study (EMBRACA) with germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer and 83 patients from a nonrandomized Phase 2 study (ABRAZO) in patients with germline BRCA-mutated locally advanced or metastatic breast cancer.

Very common (≥10%) adverse reactions in patients receiving TALZENNA in these clinical studies were fatigue (57%), anemia (50%), nausea (44%), neutropenia (30%), thrombocytopenia (30%), headache (27%), diarrhea (23%), vomiting (22%), alopecia (22%), abdominal pain (21%), decreased appetite (20%), leukopenia (16%) and dizziness (14%).

The overall frequency of grade 3 and 4 AEs is 66%. The most common (≥ 10%) adverse reactions of CTCAE grade ≥ 3 are anemia (35%), neutropenia (17%), and thrombocytopenia (17%).

The overall frequency of serious adverse events (SAEs) is 32%. The most common SAEs are anemia (5%), dyspnea (2%), and pleural effusion (2%).

Dose modifications (dose reductions or dose interruptions) due to any adverse reaction occurred in 62.3% of patients receiving TALZENNA. Very common adverse reactions (≥ 10%) leading to dose modifications were anemia (33%), neutropenia (16%), and thrombocytopenia (13%).

Permanent discontinuation due to an adverse reaction occurred in 4% of patients receiving TALZENNA. The most common adverse event that led to treatment discontinuation is anemia (0.6%). Adverse events associated with death occurred in 4% of patients receiving TALZENNA. The events leading to death reported in more than 1 patient were breast cancer, dyspnea, general physical health deterioration, neoplasm progression, and ovarian cancer.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The EMBRACA study, a randomized Phase 3 study with germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer includes 286 patients treated with TALZENNA and 126 patients treated with chemotherapy. Chemotherapy included capecitabine (55 patients), eribulin (50), gemcitabine (12), and vinorelbine (9). The median duration of study treatment was 6.1 months in patients who received TALZENNA and 3.9 months in patients who received chemotherapy.

The overall frequency of grade ≥ 3 adverse events is 68%. The most common (≥ 10%) adverse reactions of CTCAE grade ≥ 3 are anemia (39%), neutropenia (21%), and thrombocytopenia (15%).

The overall frequency of serious adverse events (SAEs) is 32%. The most common SAEs are anemia (6%), and pyrexia (2%).

Dose modifications (dose reductions or dose interruptions) due to any adverse reaction occurred in 66% of patients receiving TALZENNA. Common adverse reactions (≥ 5%) leading to dose modifications were anemia (38%), neutropenia (19%), thrombocytopenia (11%), and decreased platelet count (7%).

In the EMBRACA study, 13 (5%) patients in the TALZENNA arm and 7 (6%) patients in the chemotherapy arm had an adverse reaction that was the primary reason for permanent study drug discontinuation. Anemia was the only AE reported in more than 1 patient that led to discontinuation on the TALZENNA arm. AEs leading to death occurred in 2% of receiving TALZENNA. AEs leading to death included general physical health deterioration (2 patients), cerebral hemorrhage, liver disorder, neurological symptom, and veno-occlusive liver disease (1 patient each).

Table 4 summarizes the adverse reactions from the EMBRACA study.

Table 4. Adverse Reactions (≥ 1%) in Patients Treated with TALZENNA or Chemotherapy in a Randomized Phase 3 Study with Germline BRCA-Mutated, HER2-Negative Locally Advanced or Metastatic Breast Cancer (EMBRACA Study).

System Organ Class	ADR Term	TALZENNA N=286* (%)			Chemotherapy N=126 (%)		
		All Grades**	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Blood and lymphatic system disorders	Anemia[a]	53	39	1	18	4	1
	Thrombocytopenia[b]	27	11	4	7	2	0
	Neutropenia[c]	35	18	3	43	20	15
	Leukopenia[d]	17	6	<1	14	6	2
	Lymphopenia[e]	7	3	0	3	0	1
Metabolism and nutrition disorders	Decreased appetite	21	<1	N/A	22	1	N/A
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
	Diarrhea	22	1	0	26	6	0
	Vomiting	25	2	0	23	2	0
	Abdominal pain[f]	19	1	N/A	21	3	N/A
	Dyspepsia	10	0	N/A	7	0	N/A
	Stomatitis	8	0	0	6	0	0
Skin and subcutaneous tissue disorders	Alopecia[g]	25	N/A	N/A	28	N/A	N/A
General disorders and administration site conditions	Fatigue[h]	62	3	N/A	50	5	N/A

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

* All patients who received any dose of study drug

** There were no Grade 5 adverse drug reactions

a. Includes preferred terms of anemia, hematocrit decreased, and hemoglobin decreased.

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

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

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

e Includes preferred terms lymphocyte count decreased, lymphopenia

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

g. For talazoparib Grade 1 is 23% and Grade 2 is 2%.

h. Includes the preferred terms of fatigue or asthenia.

8.3 Less Common Clinical Trial Adverse Reactions

All ADVERSE REACTIONS occurred at > 1% and are presented in Table 4, ADVERSE REACTIONS, Clinical Trial Adverse Reactions

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Tables 5 and 6 summarize the hematologic and chemistry laboratory parameters by grade in patients treated with TALZENNA or chemotherapy from the EMBRACA study.

Table 5 Summary of Postbaseline Hematology Laboratory Parameters by Toxicity Grade reported in > 10% of patients (EMBRACA Study)

	EMBRACA Study			
	Talazoparib N=286* (%)		Chemotherapy N=126 (%)	
Parameter	**Grades 1-4**	**Grade 3 or 4**	**Grades 1-4**	**Grade 3 or 4**
Decrease in hemoglobin	90	39	77	6
Decrease in platelets	55	15	29	2
Decrease in neutrophils	68	21	70	38
Decrease in lymphocytes	76	18	53	9
Decrease in leukocytes	84	14	73	25

Abbreviation: N=number of patients.

* All patients who received any dose of study drug

Table 6 Summary of Postbaseline Chemistry Laboratory Parameters by Toxicity Grade reported in > 10% of patients (EMBRACA Study)

	EMBRACA Study			
	Talazoparib N=286* (%)		Chemotherapy N=126 (%)	
Parameter	**Grades 1-4**	**Grade 3 or 4**	**Grades 1-4**	**Grade 3 or 4**
Increase in glucose†	54	2	51	2
Increase in aspartate aminotransferase	37	2	48	3
Increase in alkaline phosphatase	36	2	34	2
Increase in alanine aminotransferase	33	1	37	2
Decrease in calcium	28	1	16	0
Decrease in glucose†	13	<1	5	0
Increase in bilirubin	10	1	11	1

Abbreviation: N=number of patients.

* All patients who received any dose of study drug

† This number represents non-fasting glucose.

9 DRUG INTERACTIONS

9.2 Overview

Talazoparib is a substrate for drug transporters P-gp and BCRP and mainly eliminated by renal clearance as unchanged compound.

9.4 Drug-Drug Interactions

Agents that may affect talazoparib plasma concentrations

Effect of P-gp inhibitors
Data from a drug-drug interaction study in patients with advanced solid tumors 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. Population pharmacokinetic (PK) analysis has shown that concomitant use of strong P-gp inhibitors with TALZENNA increased talazoparib exposure by 44.7%, relative to TALZENNA given alone. Concomitant use of strong P-gp inhibitors should be avoided. If patients must be coadministered 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), the TALZENNA dose should be reduced (see Section 4.2 Recommended Dose and Dosage Adjustment).

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.

Effect of P-gp inducers
Data from a drug-drug interaction study in patients with advanced solid tumors indicated that coadministration of single 1 mg talazoparib dose with multiple daily doses of a P-gp inducer, rifampin 600 mg, with rifampin co-administered 30 minutes before talazoparib on the day of talazoparib dosing, increased talazoparib C_{max} by 37% whereas AUC_{inf} was not affected relative to a single 1 mg talazoparib dose administered alone. This is probably the net effect of both P-gp induction and inhibition by rifampin under the tested conditions in the drug-drug interaction study. No talazoparib dose adjustments are required when coadministered with rifampin. However, the effect of other P-gp inducers on talazoparib exposure has not been studied. Other P-gp inducers (including but not limited to carbamazepine, phenytoin, and St. John's wort) may decrease talazoparib exposure.

Effect of BCRP inhibitors
The effect of BCRP inhibitors on PK of talazoparib has not been studied. Concomitant use of strong BCRP inhibitors (including but not limited to curcumin, cyclosporine, and elacridar [GF120918]) should be avoided (see Section 4.2 Recommended Dose and Dosage Adjustment).

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

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 7 - Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Agents that may affect talazoparib plasma concentrations			
Strong P-gp inhibitor (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)	CT/T	Data from a drug-drug interaction study indicated that coadministration of multiple doses of a strong P-gp inhibitor, itraconazole, with TALZENNA increased talazoparib total exposure (AUC_{inf}) and peak concentration (C_{max}) by approximately 56% and 40%, respectively, relative to TALZENNA given alone. Population pharmacokinetic (PK) analysis has shown that concomitant use of strong P-gp inhibitors with TALZENNA increased talazoparib exposure by 44.7%, relative to TALZENNA given alone	If patients must be coadministered a strong P-gp inhibitor reduce the TALZENNA dose to 0.75 mg once daily

Strong P-gp inducers (including but not limited to carbamazepine, rifampin, and St. John's wort)	CT/T	Data from a drug-drug interaction study indicated that coadministration of multiple doses of a strong P-gp inducer, rifampin, increased talazoparib C_{max} by 37% with no effect on talazoparib exposure.	Coadministration of rifampin had no significant impact on talazoparib exposure. No talazoparib dose adjustments are required when coadministered with rifampin. However, the effect of other P-gp inducers on the PK of talazoparib has not been studied. Other P-gp inducers (including but not limited to carbamazepine, phenytoin, and St. John's wort) may decrease talazoparib exposure.
Strong BCRP inhibitors (including but not limited to curcumin, cyclosporine, and elacridar [GF120918])	T	The effect of BCRP inhibitors on PK of talazoparib has not been studied.	Concomitant use of strong BCRP inhibitors should be avoided
Acid-reducing agents including proton pump inhibitors (PPI), histamine receptor 2 antagonists (H_2RA), or other acid-reducing agents	CT	Population PK analysis indicates that coadministration of acid-reducing agents had no significant impact on the absorption of talazoparib	Coadministration of acid-reducing agents had no significant impact on the absorption of talazoparib.

Legend: CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Food intake decreased the rate but not the extent of talazoparib absorption. Based on these results, TALZENNA can be administered with or without food (see Section 10.3 Pharmacokinetics, Absorption, the effect of food).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

TALZENNA is an inhibitor of poly(adenosine diphosphate [ADP] ribose) polymerase (PARP) enzymes, PARP1, and PARP2. PARP enzymes are involved in cellular DNA damage response signaling pathways such as DNA repair, gene transcription, cell cycle regulation, and cell death. PARP inhibitors (PARPi) exert cytotoxic effects on cancer cells by 2 mechanisms, inhibition of PARP catalytic activity and by PARP trapping, whereby PARP protein bound to a PARPi does not readily dissociate from a DNA lesion, thus preventing DNA repair, replication, and transcription and ultimately leading to apoptosis and/or cell death. Treatment of cancer cell lines that are harboring defects in DNA repair genes with talazoparib single agent leads to double strand DNA breaks, resulting in decreased cell proliferation and increased apoptosis. The cytotoxicity observed with talazoparib against multiple tumor cell lines harboring mutations in the DNA damage response pathways, can be attributed to its inhibition of PARP catalytic activity and PARP trapping. Talazoparib anti-tumor activity was also observed in the patient-derived xenograft BRCA1 or BRCA2-mutant breast cancer models.

10.2 Pharmacodynamics

Cardiac electrophysiology

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

10.3 Pharmacokinetics

Talazoparib exposure generally increased proportionally with dose across the range of 0.025 mg to 2 mg after daily administration of multiple doses. Following repeated daily dosing of 1 mg talazoparib to patients, the geometric mean area under the plasma concentration-time curve (AUC) and maximum observed plasma concentration (C_{max}) of talazoparib at steady-state was in the range of 126 ng•hr/mL to 208 ng•hr/mL and 11.4 ng/mL to 19.1 ng/mL, respectively. Following repeated daily dosing, talazoparib plasma concentrations reached steady-state within 2 to 3 weeks. The median accumulation ratio of talazoparib following repeated oral administration of 1 mg once daily was in the range of 2.33 to 5.15.

Table 8 - Summary of Talazoparib Pharmacokinetic Parameters in Patients with Advanced Cancer

	C_{max} (ng/mL)[a]	T_{max} (h)[c]	$t_{½}$ (h)[b]	AUC_{inf} (ng·h/mL)[a]	CL/F (L/h)[a]	V_z/F (L)[a]
Single dose mean	4.35 to 8.79	1.0 (0.5-2.0)	62.4 to 89.8	116 to 196	5.12 to 7.71	447 to 847

Summary statistics based on pharmacokinetic parameters of talazoparib following administration of a single 1 mg dose of talazoparib from 4 studies in cancer patients.

[a] For C_{max}, AUC, CL/F, and V_z/F geometric mean is shown

[b] For $t_{½}$ mean range is shown

[c] For t_{max} median (range) is shown

Absorption: Following oral administration of talazoparib, the median time to C_{max} (T_{max}) was generally between 1 to 2 hours after dosing under fasting conditions. An absolute bioavailability study has not been conducted in humans. However, based on urinary excretion data the absolute bioavailability is at least 54.6% with fraction absorbed of at least 68.7% (see Elimination).

The effect of food

Food intake decreased the rate but not the extent of talazoparib absorption. Following a single oral dose of talazoparib with high-fat, high-calorie food (approximately 827 calories, 57% fat), the mean C_{max} of talazoparib was decreased by approximately 46%, the median T_{max} was delayed from 1 to 4 hours, while the AUC_{inf} was not affected. Based on these results, TALZENNA can be administered with or without food.

Distribution: The population mean apparent volume of distribution (V_{ss}/F) of talazoparib was 420 L. In vitro, talazoparib is approximately 74% bound to plasma proteins with no concentration dependence over the concentration range of 0.01 µM to 1 µM. Renal or hepatic impairment does not appear to impact talazoparib protein binding as there was no obvious trend in the mean talazoparib fraction of unbound drug (f_u) in human plasma in vivo with worsening renal or hepatic function.

Metabolism: Talazoparib undergoes minimal hepatic metabolism in humans. Following oral administration of a single 1 mg dose of [^{14}C]talazoparib to humans, no major circulating metabolites were identified in plasma, and talazoparib was the only circulating drug-derived entity identified. No metabolites that individually represented more than 10% of the administered dose were recovered in the urine or feces. 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.

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

In vitro, talazoparib did not inhibit any of the major intestinal, hepatic or renal membrane transporters (P-gp, BCRP, organic anion transporting polypeptide [OATP]1B1, OATP1B3, organic cationic transporter [OCT]1 OCT2, organic anion transporter [OAT]1, OAT3, bile salt export pump [BSEP], multidrug and toxin extrusion [MATE]1 and MATE2-K) at clinically relevant concentrations.

In vitro, talazoparib did not inhibit any of the major uridine-diphosphate glucuronosyltransferase (UGT) isoforms (1A1, 1A4, 1A6, 1A9, 2B7, and 2B15) at clinically relevant concentrations.

Elimination: 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. In 6 female patients with advanced solid tumors given a single oral dose of [^{14}C]talazoparib, a mean of 68.7% and 19.7% of the total administered radioactive dose was recovered in urine and feces, respectively. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 54.6% of the administered dose, while unchanged talazoparib recovered in the feces accounted for 13.6%.

Special Populations and Conditions

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

Age: 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) on the PK of talazoparib. The results have shown that age had no clinically relevant effect on the PK of talazoparib.

Sex: A population PK analysis was conducted using data from 490 patients with cancer to evaluate the impact of sex (53 males and 437 females) on the PK of talazoparib. The results have shown that sex had no clinically relevant effect on the PK of talazoparib.

Pregnancy and Breast-feeding: There are no data from the use of TALZENNA in pregnant women. Studies in animals have shown genotoxicity and embryo-fetal toxicity (see Section ~~13~~ 16 Non-Clinical Toxicology). TALZENNA can cause fetal harm when administered to a pregnant woman. It is unknown whether TALZENNA is excreted in human breast milk. A risk to newborns/infants cannot be excluded and therefore breastfeeding is not recommended during treatment with TALZENNA and for at least 1 month after the final dose.

Race: A population PK analysis was conducted using data from 490 patients with cancer to evaluate the impact of race (361 White, 41 Asian, 16 Black, 9 Others, and 63 Not reported) on the PK of talazoparib. The results have shown that ethnicity had no clinically relevant effect on the PK of talazoparib.

Hepatic Insufficiency: Based on a population PK analysis that included 490 patients, where 118 patients had mild hepatic impairment (total bilirubin ≤ 1.0 × ULN and AST > ULN, or total bilirubin > 1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the PK of talazoparib. The PK of talazoparib in patients with normal hepatic function, mild hepatic impairment, moderate hepatic impairment (total bilirubin >1.5 to 3.0 × ULN and any AST), or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST) was studied in a PK trial. Population PK analysis using data from this PK trial indicated that mild, moderate, or severe hepatic impairment had no significant impact on the PK of talazoparib.

Renal Insufficiency: Data from a PK trial in advanced cancer patients with varying degrees of renal impairment indicate that talazoparib total exposure (AUC_{0-24}) after multiple talazoparib once-daily doses did not change and increased by 85%, and 167% in patients with mild (60 mL/min ≤ CrCL <90 mL/min), moderate (30 mL/min ≤ CrCL <60 mL/min) and severe (15 mL/min ≤ CrCL < 30 mL/min) renal impairment, respectively, relative to patients with normal renal function (CrCL ≥90mL/min). Talazoparib C_{max} increased by 8%, 86%, and 93% in patients with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function. Consistent with these findings, a population PK analysis that included 490 patients, where 132 patients had mild renal impairment, 33 patients had

moderate renal impairment, and 1 patient had severe renal impairment, showed that talazoparib CL/F was decreased by 14.4% and 37.1% in patients with mild and moderate renal impairment, corresponding to 17% and 59% increase in AUC, respectively, when compared to patients with normal renal function. The PK of talazoparib has not been studied in patients requiring hemodialysis.

Obesity: A population PK analysis was conducted using data from 490 patients with cancer to evaluate the impact of body weight (ranging from 35.7 kg to 162 kg) on the PK of talazoparib. The results have shown that body weight had no clinically relevant effect on the PK of talazoparib.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C to 30°C. Maintain in original bottle to protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

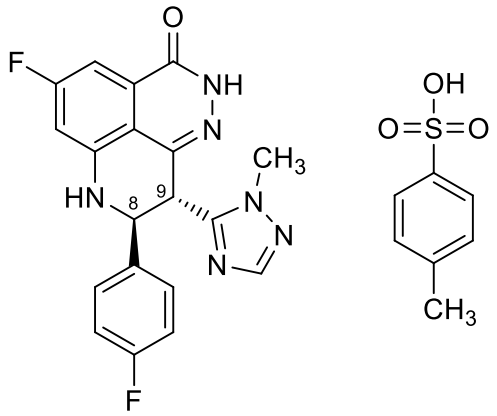
Drug Substance

Proper name/common name: Talazoparib tosylate

Chemical name: (8*S*,9*R*)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-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)

Molecular formula is $C_{19}H_{14}F_2N_6O$ for the free base and $C_{26}H_{22}F_2N_6O_4S$ for the tosylate salt; molecular mass is 380.35 Daltons for the free base and 552.56 Daltons for the tosylate salt

Structural formula:



Physicochemical properties: talazoparib tosylate is a white to yellow, non-hygroscopic crystalline solid; free base aqueous solubility ranges from 0.03 mg/mL to 0.01 mg/mL across the physiological pH range.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 9 - Summary of patient demographics for clinical trials in patients with germline breast cancer susceptibility gene (BRCA)-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
EMBRACA	open-label, randomized, parallel, 2-arm multicenter study	1 mg capsules taken orally once daily or chemotherapy at standard doses until progression or unacceptable toxicity	TALZENNA n= 287[a, b] Chemotherapy n= 144	45 years (27 – 84)	98% Female

[a] All patients randomized in the study
[b] All patients who received any dose of study drug (N=286), Section 8.2 Clinical Adverse Drug Reactions

EMBRACA Study
The efficacy and safety of TALZENNA was demonstrated in an open-label, randomized, parallel, 2-arm multicenter study of TALZENNA versus physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, vinorelbine) in patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer who received no more than 3 prior cytotoxic chemotherapy regimens for their metastatic or locally advanced disease. Patients were required to have received prior chemotherapy treatment with an anthracycline and/or a taxane (unless contraindicated) in the neoadjuvant, adjuvant and/or metastatic setting. Patients with prior platinum therapy for advanced disease were required to have no evidence of disease progression during platinum therapy and no relapse within 6 months. A majority (>90%) of patients with hormone receptor-positive (HR+) breast cancer were treated with a prior endocrine-based therapy. No prior treatment with a PARP inhibitor was permitted.

A total of 431 patients were randomized 2:1 to receive TALZENNA 1 mg capsules once daily or physician's choice chemotherapy at standard doses until progression or unacceptable toxicity. Of the 431 patients randomized onto EMBRACA, 287 were randomized to the TALZENNA arm and 144 to the chemotherapy arm. Randomization was stratified by prior use of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status (triple-negative breast cancer [TNBC] versus non-TNBC), and history of central nervous system metastasis (yes versus no). The majority of patients 408/431 (95%) were selected using the BRAC*Analysis* test and BRCA mutation status (breast cancer susceptibility gene 1 [BRCA1] positive or breast cancer susceptibility gene 2 [BRCA2] positive) was similar across both treatment arms.

Patient demographic and baseline characteristics were generally similar between the study treatment arms. 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 TALZENNA 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 randomized patients, 1% versus

2% were males, 66.9% versus 75.0% were White; 10.8% versus 11.1% were Asian, and 4.2% versus 0.7% were Black or African American in the TALZENNA and chemotherapy arms, respectively. Almost all patients (97.7%) in both arms had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Approximately 55.9% of patients had hormone receptor-positive (either estrogen receptor [ER]-positive- or progesterone receptor [PR]-positive) disease; 44.1% of patients had triple-negative disease and the proportions were balanced across treatment arms. The median time from initial diagnosis of breast cancer to diagnosis of advanced breast cancer was 1.9 years (range 0 to 22) on the TALZENNA arm and 2.7 years (range 0 to 24) on the chemotherapy arm. The reported disease-free interval (DFI) was < 12 months in 37.6% of patients on the TALZENNA arm and in 29.2% of patients on the chemotherapy arms. Among all patients enrolled, the median number of prior cytotoxic regimens for advanced breast cancer was 1 where 38.3% of patients received no prior regimens for advanced or metastatic disease, 37.4% received 1, 19.7% received 2 and 4.6% received > 3 prior regimens, respectively. Sixteen percent of patients in the TALZENNA arm and 20.8% of patients in the chemotherapy arm had received prior platinum treatment.

14.2 Study Results

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

The study met its primary objective of demonstrating a statistically significant improvement in PFS for TALZENNA compared with chemotherapy (hazard ratio [HR] 0.54; 95% confidence interval [CI]: 0.41, 0.71; p-value < 0.0001). A sensitivity analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results. There was no statistically significant effect on OS at the time of final OS analysis. Efficacy data for EMBRACA are summarized in Table 10 and the Kaplan-Meier curve for PFS is shown in Figure 1 and final OS in Figure 3. Consistent results for PFS were observed across pre-specified patient subgroups, upon which randomization of patients was stratified (Figure 2).

Table 10. Summary of Efficacy Results – EMBRACA Study*

	TALZENNA	Chemotherapy
PFS by BICR	N=287	N=144
Events, number (%)	186 (65%)	83 (58%)
Median (95% CI), months	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard ratio** (95% CI)[d]	0.54 (0.41, 0.71)	
2-sided p-value[a]	p< 0.0001	
Confirmed Objective Response by Investigator[c]	N=219	N=114
ORR, % (95% CI)	50.2 (43.4, 57.0)	18.4 (11.8, 26.8)
Duration of Response by Investigator	N=110	N=21
Median (95% CI), months	6.4 (5.4, 9.5)	3.9 (3.0, 7.6)
OS (final analysis)[b]		
Events, number (%)	216 (75.3%)	108 (75.0%)
Median, months (95% CI)	19.3 (16.6, 22.5)	19.5 (17.4, 22.4)
Hazard ratio** (95% CI)	0.85 (0.67, 1.07)	
2-sided p-value[a]	p=0.1693	

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CR=complete response; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; RECIST 1.1=response Evaluation Criteria in Solid Tumors version 1.1; SD=stable disease.

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

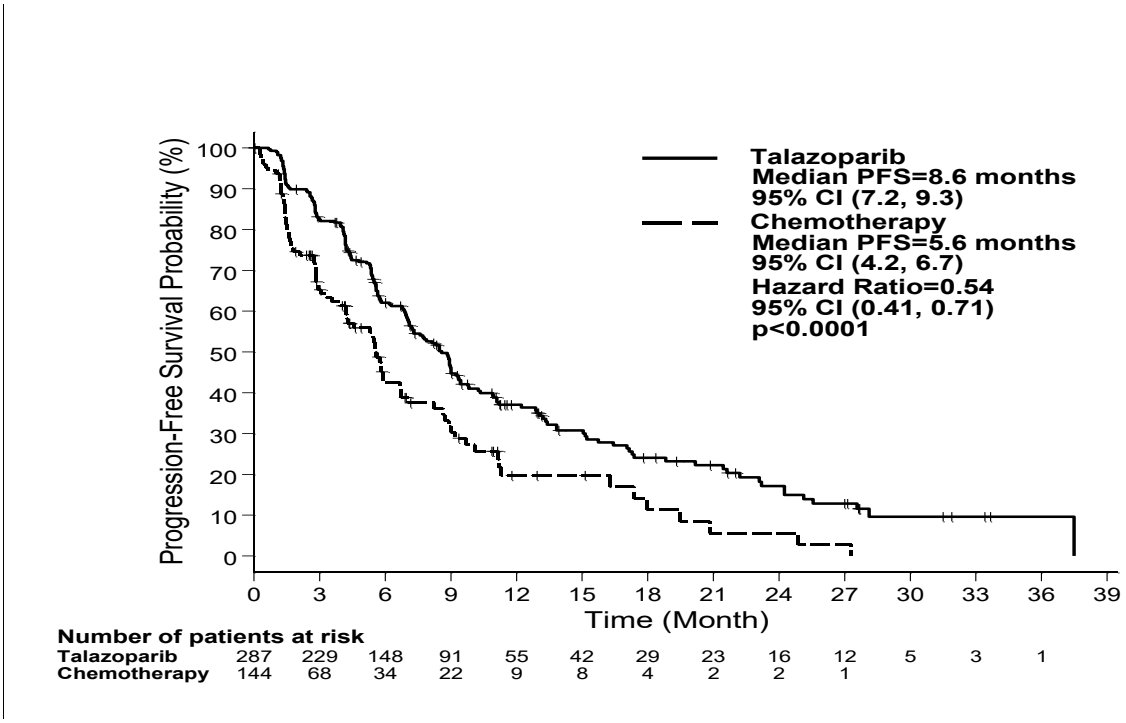
** Hazard ratio was based on stratified Cox regression model with treatment as the only covariate (stratification factors: number of prior cytotoxic chemotherapy regimens, triple-negative status, history of central nervous system metastasis) and was relative to overall chemotherapy with < 1 favouring talazoparib.

a. Stratified Log-rank test.

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

c. Conducted in ITT with measurable disease population. The complete response rate was 5.5% for TALZENNA compared to 0% for the chemotherapy arm.

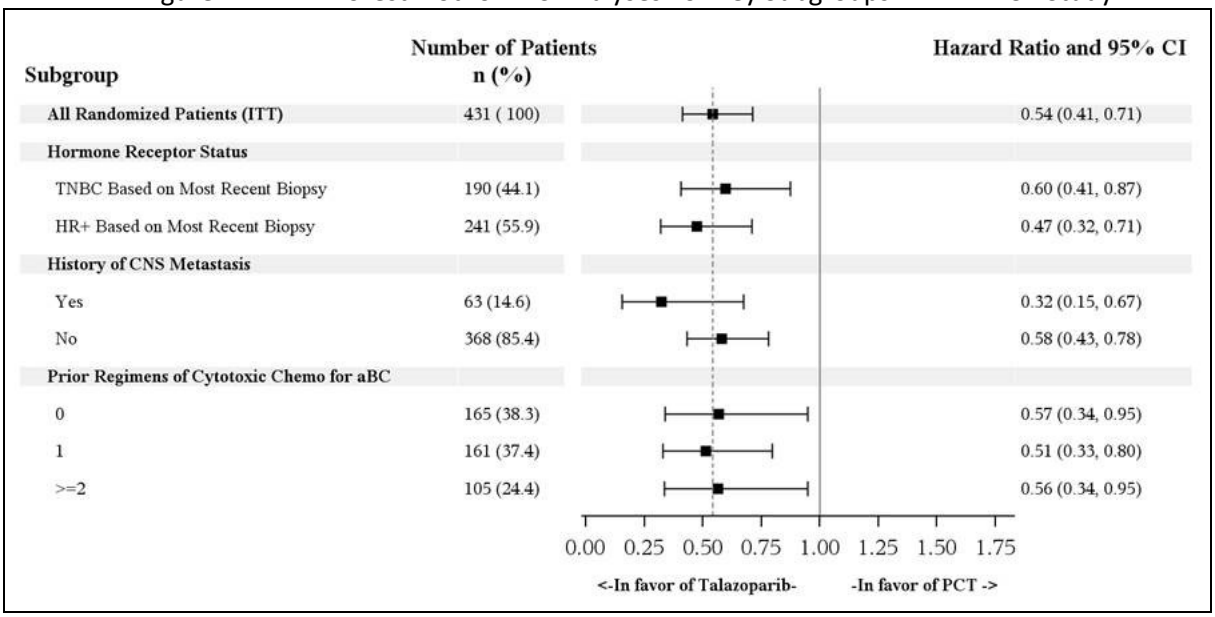
Figure 1. Kaplan-Meier Curves of PFS by BICR – EMBRACA Study



Primary analysis p-value was based on a stratified log-rank test. Hazard ratio was based on stratified Cox regression model with treatment as the only covariate (stratification factors: number of prior cytotoxic chemotherapy regimens, triple-negative status, history of central nervous system metastases) and was relative to overall chemotherapy with <1 favoring TALZENNA.

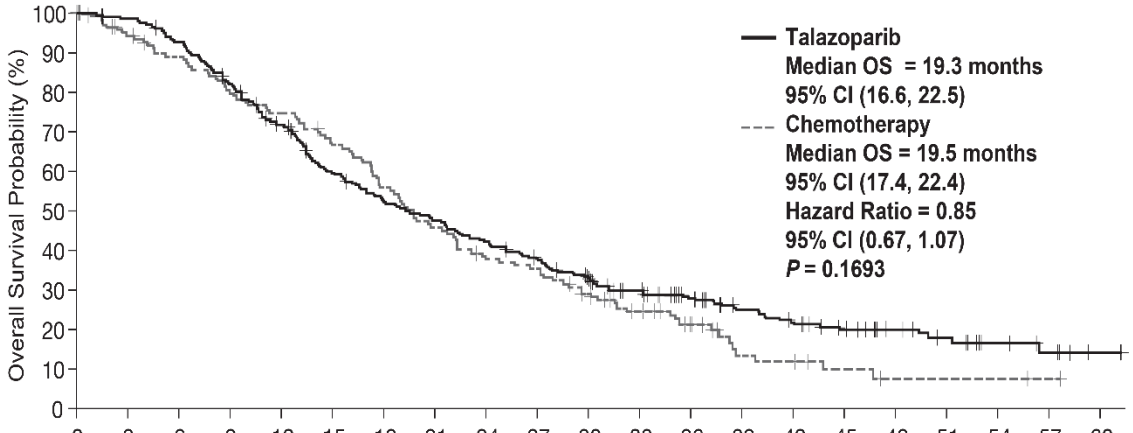
Abbreviations: BICR = blinded independent central review; CI=confidence interval; PFS=progression-free survival.

Figure 2. Forest Plot for PFS Analyses For Key Subgroups – EMBRACA Study



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

Figure 3 Kaplan-Meier Curves of OS - EMBRACA study



Number of patients at risk																					
Talazoparib	287	280	264	232	199	163	143	128	113	101	85	68	54	41	35	27	20	15	9	6	2
Chemotherapy	144	125	116	105	96	86	71	58	48	44	34	25	18	8	7	4	2	2	2	1	0

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

15 MICROBIOLOGY

This section is not applicable

16 NON-CLINICAL TOXICOLOGY

General Toxicology (single and repeat-dose studies)

In repeat-dose toxicity studies of up to 13-week duration, talazoparib was clinically tolerated in rats at 0.04 mg/kg/day and in dogs at 0.01 mg/kg/day and the AUC_{24} exposure margins at the no adverse effect level are 0.2-fold the relevant human exposure. The main findings at subtherapeutic exposures included bone marrow hypocellularity with dose-dependent decrease in hematopoietic cells, depletion of lymphoid tissue in multiple organs and atrophy and/or degenerative changes in testes, epididymis, and seminiferous tubules. Additional findings at higher exposures included dose-dependent increase in apoptosis/necrosis in the gastrointestinal (GI) tract, liver, and ovary. Most of the histopathologic findings were generally reversible while the testes findings were partially reversible after 4 weeks of dosing cessation. These toxicity findings are consistent with the pharmacology of talazoparib and its tissue distribution pattern.

Carcinogenicity

Carcinogenicity studies have not been conducted with talazoparib.

Genotoxicity

In genotoxicity studies, talazoparib did not demonstrate mutagenic potential in the bacterial reverse mutation (Ames) test but 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.

Reproductive and Developmental Toxicology

In an embryo-fetal development study in rats, talazoparib administered during the period of organogenesis resulted in, decreased fetal weight, embryo-fetal death, fetal malformation (depressed eye bulge, small eye, split sternebra, fused cervical vertebral arch) and structural variations in bones (misshapen zygomatic arch, incompletely ossified, split or misshapen sternebrae, supernumerary ribs, incompletely ossified, fused and/or misshapen cervical arch) at a maternal systemic AUC_{24} exposure approximately 0.09-fold the relevant human exposure at the recommended dose.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTALZENNA®

Talazoparib Capsules

Read this carefully before you start taking **TALZENNA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TALZENNA.**

Serious Warnings and Precautions

- Take **TALZENNA** under the care of a doctor who knows how to use anti-cancer drugs.
- **Myelodysplastic Syndrome or Acute Myeloid Leukemia:** Serious bone marrow problems such as Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) have been reported in patients who received PARP inhibitors, including TALZENNA. MDS or AML can lead to death.
- TALZENNA can harm your unborn baby if you take it when you are pregnant.

What is TALZENNA used for?
TALZENNA is taken by itself to treat a specific type of breast cancer (known as human epidermal growth factor receptor 2 [HER2]-negative) in adults:

- who have mutations (changes) in certain genes called BRCA (known as the breast cancer gene),
- who have had previous chemotherapy for your breast cancer and
- whose cancer has spread beyond the original tumor or to other parts or organs of the body.

Before taking TALZENNA, a test will be performed. This test is to confirm that your disease is suitable for treatment with this drug.

How does TALZENNA work?
TALZENNA is a type of drug called a PARP inhibitor. PARP inhibitors block a protein called poly [adenosine diphosphate-ribose] polymerase (PARP). This protein helps cells to repair their damaged DNA. Blocking PARP activity prevents the repair of damaged DNA in cancer cells leading to cell death.

What are the ingredients in TALZENNA?
Medicinal ingredients: talazoparib, as talazoparib tosylate
Non-medicinal ingredients: hydromellose, pharmaceutical grade printing ink, red iron oxide, silicified microcrystalline cellulose, titanium dioxide and yellow iron oxide

TALZENNA comes in the following dosage forms:
Capsules: 0.25 mg and 1 mg

Do not use TALZENNA if:

- you are allergic to talazoparib tosylate or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TALZENNA. Talk about any health conditions or problems you may have, including if you:

- have or have had liver or kidney problems.

Other warnings you should know about:

Children and adolescents:

- TALZENNA is not recommended for use in patients under the age of 18 years.

Driving and using machines:

- Before you do tasks which may require special attention, wait until you know how you respond to TALZENNA. If you feel dizzy, weak or tired, do not drive or use tools or machines.

Low blood-cell counts:

- TALZENNA may lower your blood cell counts such as your platelets (thrombocytopenia), red blood cells (anemia) and white blood cells (neutropenia).

Pregnancy, breastfeeding and fertility – information for women and men:

- If you or your partner are pregnant, or still able to get pregnant and/or breastfeed, there are specific risks you must discuss with your healthcare professional.

  Pregnancy – information for women
  - A pregnancy test should be done before you start to take TALZENNA.
  - Avoid becoming pregnant while taking TALZENNA. It may harm your unborn child or make you lose the pregnancy.
  - If you become pregnant while taking TALZENNA, tell your doctor right away.
  - If you plan to get pregnant after taking your dose of TALZENNA, ask your doctor for advice. This is because TALZENNA may remain in your body after the last dose.

  Pregnancy – information for men
  - If your partner becomes pregnant while you are taking TALZENNA, tell your partner's doctor right away.

  Birth Control – information for women and men
  - Use an effective method of birth control while taking TALZENNA.
  - Talk to your doctor about birth control methods that may be right for you.
  - Men taking TALZENNA must use a condom because the drug may pass into the sperm. Do NOT donate sperm while taking TALZENNA.
  - Women should NOT donate eggs while taking TALZENNA.
  - **After you finish treatment with TALZENNA:**
    - **Women who are able to become pregnant:** Keep using birth control and do NOT donate eggs for 7 months after taking your last dose.
    - **Males with female partners who are pregnant or able to become pregnant:** Keep using birth control and do NOT donate sperm for 4 months after taking your last dose.

  Breastfeeding – information for women
  - TALZENNA may pass into breast milk. Do not breast-feed while you are taking it and for 1

month after taking your last dose of TALZENNA. Talk to your doctor about the best way to feed your baby.

Fertility – information for women and men

- TALZENNA may affect your fertility. Talk to your doctor if this is a concern for you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TALZENNA:

- clarithromycin, erythromycin – used to treat bacterial infections
- itraconazole, ketoconazole – used to treat fungal infections
- darunavir, indinavir, lopinavir, saquinavir, ritonavir, tipranavir – used to treat viral infections, primarily HIV
- amiodarone, dronedarone, propafenone – used to treat illnesses with rapid heart beat
- verapamil, carvedilol – used to treat high blood pressure
- quinidine – used to treat abnormal heart rhythms
- lapatinib – used to treat certain types of cancer
- carbamazepine – used to treat seizures and epilepsy
- St John's Wart (Hypericum perforatum) – an herbal remedy used mainly for depression
- rifampin – used to treat bacterial infections, primarily tuberculosis
- curcumin – an herbal supplement
- cyclosporine – used to suppress the immune system

How to take TALZENNA:

- Take TALZENNA exactly as your healthcare professional has told you. Check with your doctor, pharmacist or nurse if you are not sure.
- Do not change your dose or stop taking TALZENNA without first talking with your doctor.
- Take TALZENNA with or without food at about the same time each day.
- Swallow TALZENNA capsules whole. Do NOT chew, crush, open or dissolve TALZENNA capsules.
- Do NOT touch or handle crushed or broken TALZENNA capsules.
- If you vomit after taking your dose, take your next dose at your regular time.

Usual dose:

Usual adult dose:
1 mg: Take one 1 mg capsule by mouth once a day.

Your doctor may change your dose of TALZENNA or tell you to stop taking it. This may happen if:

- you have certain side effects while taking TALZENNA.
- you are taking medicines that may interact with TALZENNA.

Reduced adult dose:
0.75 mg: Take three 0.25 mg capsules by mouth once a day
0.5 mg: Take two 0.25 mg capsules by mouth once a day
0.25 mg: Take one 0.25 mg capsule by mouth once a day

Overdose:

If you think you have taken too much TALZENNA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take TALZENNA, take your next dose at your regular time. Do not take an extra dose to make up for a missed dose.

What are possible side effects from using TALZENNA?

These are not all the possible side effects you may feel when taking TALZENNA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects of TALZENNA may include:

- decreased appetite
- diarrhea
- nausea (feeling the need to vomit)
- vomiting (throwing up)
- dizziness
- changes in the way food tastes
- indigestion or heartburn
- upset stomach
- hair loss
- fatigue (feeling tired or weak)
- inflamed and sore mouth

TALZENNA can cause abnormal blood test results. This includes decreased blood cell counts. Your healthcare professional will test your blood before you start treatment with TALZENNA. They will then test your blood every month while you are taking TALZENNA for the first year. Your doctor will tell you if your test results are abnormal and may adjust your treatment to correct these side effects.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Anemia (low red blood cell count): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness, headaches, dizziness.		X	
Leukopenia (low white blood-cell count: leukophils): fever or infection, fatigue, aches and pains, and flu-like symptoms.		X	
Lymphopenia (low white blood-cell count: lymphocytes): Get infections more easily.		X	
Neutropenia (low white blood-cell count): infections, chills, fever, fatigue, aches, pains and flu-like symptoms.		X	
Thrombocytopenia (low blood platelet count): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness.		X	
COMMON			
Headache	X		
Abdominal Pain: pain in the stomach.	X		
UNCOMMON			
Myelodysplastic Syndrome or **Acute Myeloid Leukemia** (a group of diseases in which the body produces large numbers of abnormal blood cells): Fever, infection, bruising or bleeding easily, breathlessness, blood in urine or stool.			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store between 15°C to 30°C. Maintain in original bottle to protect from light.
- Do not use after the expiry date stated on the bottle after EXP.
- Do not throw away any medicines via wastewater or household waste. Ask your healthcare provider or pharmacist about the right way to throw away outdated or unused TALZENNA. These measures will help protect the environment.
- **Keep out of reach and sight of children.**

If you want more information about TALZENNA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (www.pfizer.ca), or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC

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