PDL DRUG REVIEW

Proprietary Name: Talzenna®
Common Name: talazoparib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Lynparza	Non-Recommended with Conditions

Summary

Pharmacology/Usage: Talazoparib, the active ingredient of Talzenna®, is an inhibitor of mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme, including PARP1 and PARP2, which play a role in DNA repair. In vitro studies with cancer cell lines that harbored defects in DNA repair genes, including BRCA 1 and 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.

Indication: For the treatment of adults with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (*gBRCAm*) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for Talzenna®.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Talzenna® can cause embryo-fetal harm when given to a pregnant woman. There are no available data on use during pregnancy to inform a drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to starting treatment and advise them to use effective contraception during treatment and for at least 7 months after the last dose. In addition, advise male partners with female partners of reproductive potential and pregnant partners to use effective contraception during treatment and for at least 4 months after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Capsules: 0.25mg, 1mg. Swallow whole and capsules must not be opened or dissolved.

Recommended Dosage: Select patients for the treatment of advanced breast cancer with Talzenna® based on the presence of germline BRCA mutations. Information on the FDA-approved test for the detection of BRCA mutations is available at http://www.fda.gov/companiondiagnostics.

Take 1mg PO QD, with or without food until disease progression or unacceptable toxicity occurs. For patients with moderate renal impairment, the recommended dose is 0.75mg PO QD. Dose adjustments are not required with mild renal impairment, and use has not been studied in patients with severe renal impairment or patients requiring hemodialysis. While does adjustments are not required for patients with mild hepatic impairment, use has not been studied in patients with moderate or severe hepatic impairment.

To manage adverse reactions, consider interruption of treatment, with or without dose reductions based on severity and clinical presentation. Refer to the prescribing information for additional information. In addition, it is recommended to monitor complete blood counts monthly and as clinically indicated. Refer to the prescribing information for information on dose modification and management with abnormal laboratory values, including hemoglobin, platelet counts, ad neutrophil counts.

Drug Interactions: Coadministration with BCRP inhibitors may increase talazoparib levels. If concomitant use cannot be avoided, monitor patients for the potential for increased adverse reactions when coadministered.

Coadministration of P-gp inhibitors may increase talazoparib exposure. In clinical studies, coadministration of P-gp inhibitors, including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil, resulted in about a 45% increase in talazoparib exposure and an increase in the rate of Talzenna® dose reduction. If coadministration with these P-gp inhibitors cannot be avoided, reduce the Talzenna® dose (reduce to 0.75mg PD). When the P-gp inhibitor is discontinued, increase the Talzenna® dose to the dose used prior to the start of the P-gp inhibitor. When co-administering Talzenna® with P-gp inhibitors not listed above, monitor patients for potential increased adverse reactions.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Talzenna® for all grades) minus reported % incidence for chemotherapy in ≥20% of patients receiving Talzenna®. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than comparator.* The most frequently reported adverse event included anemia (35%), neutropenia (0%), thrombocytopenia (20%), decreased appetite (0%), headache (11%), nausea (2%), vomiting (2%), diarrhea (0%), alopecia (0%), and fatigue (12%). Laboratory abnormalities included decrease in hemoglobin (13%), decrease in leukocytes (11%), decrease in neutrophils (0%), decrease in lymphocytes (23%), decrease in platelets (26%), increase in glucose (3%), increase in aspartate aminotransferase (0%), increase in alkaline phosphatase (2%), increase in alanine aminotransferase (0%), and decrease in calcium (12%).

The following were reported in <20% receiving Talzenna® and were not compared with chemotherapy: abdominal pain (19%), dizziness (17%), leukopenia (17%), dysgeusia (10%), dyspepsia (10%), stomatitis (8%), and lymphopenia (7%).

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 patients treated with Talzenna® in clinical studies, and the duration of treatment in these 2 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. Do not start Talzenna® until patients have adequately recovered from hematologic toxicity caused by previous chemotherapy. It is recommended to monitor complete blood counts for cytopenia at baseline and monthly thereafter. With prolonged hematological toxicities, interrupt Talzenna® and monitor blood counts weekly until recovery. If MDS/AML is confirmed, discontinue treatment.

Myelosuppression consisting of anemia, leukopenia/neutropenia, and/or thrombocytopenia, have been reported in patients treated with Talzenna®. Grade ≥3 anemia, neutropenia, and thrombocytopenia were reported, respectively, in 39%, 21%, and 15% of patients receiving Talzenna®. Monitor complete blood count for cytopenia at baseline and monthly thereafter. Do not start Talzenna® until patients have adequately recovered from hematological toxicity caused by previous therapy.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Pfizer

Analysis: The safety and efficacy of Talzenna® were assessed in an open-label study (EMBRACA study) that included patients (N=431) with gBRCAm HER2-negative locally advanced or metastatic breast cancer who were randomized to Talzenna® or healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. Patients were required to have received treatment with an

anthracycline and/or a taxane (unless contraindicated) in the neoadjuvant, adjuvant, and/or metastatic treatment setting. First-line treatment for advanced or metastatic disease with no prior adjuvant chemotherapy was allowed if the investigator determined that 1 of the 4 chemotherapy choices in the control arm would be an appropriate treatment option for the patient. No prior treatment with a PARP inhibitor was allowed.

Of the patients, 408 (95%) were centrally confirmed to have a deleterious or suspected deleterious gBRCAm. BRCA mutation status was similar across treatment arms. The median age of patients treated with Talzenna® was 45 years (range 27 to 84) vs 50 years for patients treated with chemotherapy (range 24 to 88). Of the randomized patients, 67% vs 75% were white and 1 vs 2% were males. In addition, approximately 98% in both treatment groups had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and about 15% taking Talzenna® and 14% taking chemotherapy had a history of CNS metastases.

The main efficacy outcome was progression-free survival (PFS) evaluated per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by blinded independent central review (BICR). Results suggested that a statistically significant improvement in PFS was seen for the Talzenna® group as compared with chemotherapy. The overall survival (OS) data were not mature at the time of the final PFS analysis. Results can be seen in the table below, which was adapted from the prescribing information.

	Talzenna®	Chemotherapy
Progression-Free Survival (PFS) by BICR	N=287	N=144
Events, number (%)	186 (65%)	83 (58%)
Median months	8.6	5.6
Hazard Ratio (HR), p-value	0.54; p<0.0001	
Patients with measurable disease by investigator	N=219	N=114
Objective Response Rate (ORR)	50.2%	18.4%
Duration of Response Median months	6.4	3.9

Place in Therapy: Talzenna® is an oral capsule indicated for the treatment of adults with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (*gBRCAm*) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for Talzenna®. In a clinical trial compared with chemotherapy, Talzenna® was found to demonstrate a statistically significant improvement in progression free survival compared to the provider's choice of chemotherapy.

There is some evidence to suggest, based on progression-free survival, that Talzenna® is more effective than certain chemotherapy; however, it is recommended that Talzenna® be placed on the Recommended Drug List as non-recommended and require prior authorization to confirm appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Talzenna [package insert]. New York, NY: Pfizer Labs; 2018.