Talaparib

Talazoparib Tosylate INN

Everest

COMPOSITION

TALAPARIB capsule: Each capsule contains Talazoparib Tosylate INN equivalent to Talazoparib 1 mg.

PHARMACOLOGY

Mechanism of Action

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

PHARMACODYNAMICS

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

Cardiac Electrophysiology

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

PHARMACOKINETICS

After administration of Talazoparib 1 mg orally once daily as a single agent (the recommended dosage for breast cancer), the mean [% coefficient of variation (CV%)] AUC and maximum observed plasma concentration (Cmax) of Talazoparib at steady-state was 208 (37%) ng.hr/mL and 16.4 (32%) ng/mL, respectively. The mean (CV%) steady-state Ctrough was 3.53 (61%) ng/mL. After administration of Talazoparib 0.5 mg orally once daily (the recommended dosage for prostate cancer) in combination with Enzalutamide, the mean (CV%) steady-state Ctrough ranged from 3.29 to 3.68 ng/mL (45% to 48%). The pharmacokinetics (PK) of Talazoparib is linear from 0.025 mg to 2 mg (2 times the recommended dose for breast cancer). The median accumulation ratio of Talazoparib following 1 mg orally once daily is 2.3 to 5.2. Talazoparib plasma concentrations reached steady-state within 2 to 3 weeks when administered as a single agent and within 9 weeks when coadministered with Enzalutamide.

Absorption

The median time to Cmax (Tmax) was generally between 1 to 2 hours after dosing.

Distribution

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

Elimination

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

Metabolism

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

Excretion

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

Specific Populations

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

Patients with Renal Impairment

Mild (eGFR 60 – 89 mL/min/1.73 m2) renal impairment had no clinically significant effect on Talazoparib pharmacokinetics. Talazoparib steady-state total exposure (AUC) increased by 43% in subjects with moderate (eGFR 30 – 59 mL/min/1.73 m2) renal impairment and 163% in patients with severe (eGFR 15 – 29 mL/min/1.73 m2) renal impairment relative to subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m2).

INDICATIONS AND USAGE

Talazoparib is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for:

BRCA-mutated (gBRCAm) HER2-negative Locally Advanced or Metastatic Breast Cancer

As a single agent, for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer.

HRR Gene-mutated mCRPC

In combination with Enzalutamide for the treatment of adult patients with HRR gene-mutated metastatic castration-resistant prostate cancer (mCRPC).

DOSAGE AND ADMINISTRATION

Patient Selection

gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer

For the treatment of advanced breast cancer with Talazoparib, patients should be selected based on the presence of germline BRCA mutations.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

For the treatment of HRR gene-mutated mCRPC with Talazoparib, patients should be selected based on the presence of HRR gene mutations (ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C).

Recommended Dosage for gBRCAm HER2-negative Locally Advanced or Metastatic Breast Cancer

- The recommended dosage of Talazoparib is 1 mg taken orally once daily until disease progression or unacceptable toxicity.

- For adverse reactions, dosing interruption or dose reduction should be considered.

Recommended Dosage for HRR Gene-mutated mCRPC

- The recommended dosage of Talazoparib is 0.5 mg taken orally once daily in combination with Enzalutamide until disease progression or unacceptable toxicity.

Talazoparib should be taken with or without food. Talazoparib capsules should be swallowed whole. It should not be opened or dissolved. If a patient vomits or misses a dose of Talazoparib, they should be instructed to take the next prescribed dose at the usual time.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

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

Myelosuppression
Myelosuppression consisting of anemia, neutropenia, and/or thrombocytopenia, have been reported in patients treated with Talazoparib. If hematological toxicities do not resolve within 28 days, discontinue Talazoparib and refer the patient to a hematologist for further investigations including bone marrow analysis and blood sample for cytogenetics.

Embryo-Fetal Toxicity
Based on its mechanism of action and findings from animal data, Talazoparib can cause fetal harm when administered to a pregnant woman.

Infertility
Based on animal studies, Talazoparib may impair fertility in males of reproductive potential.

SIDE EFFECTS
Most common adverse reactions (≥20%) as a single agent, including laboratory abnormalities, are: Hemoglobin decreased, neutrophils decreased, lymphocytes decreased, platelets decreased, fatigue, glucose increased, aspartate aminotransferase increased, alkaline phosphatase increased, alanine aminotransferase increased, calcium decreased, nausea, headache, vomiting, alopecia, diarrhea, and decreased appetite.

DRUG INTERACTIONS
Breast Cancer
Coadministration of Talazoparib should be avoided with the following P-gp inhibitors: itraconazole, amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil. If coadministration of Talazoparib with these P-gp inhibitors cannot be avoided, the dose of Talazoparib should be reduced. When the P-gp inhibitor is discontinued, the dose of Talazoparib should be increased.

Coadministration of Talazoparib with these P-gp inhibitors increased Talazoparib concentrations, which may increase the risk of adverse reactions.

Increased adverse reactions should be monitored and the dosage should be modified as recommended for adverse reactions when Talazoparib is coadministered with other P-gp inhibitors.

HRR Gene-mutated mCRPC
The effect of coadministration of P-gp inhibitors on Talazoparib exposure when Talazoparib is taken in combination with Enzalutamide has not been studied. Increased adverse reactions should be monitored and the dosage should be modified as recommended for adverse reactions when Talazoparib is coadministered with a P-gp inhibitor.

Effect of BCRP Inhibitors
Increased adverse reactions should be monitored and the dosage should be modified as recommended for adverse reactions when Talazoparib is coadministered with a BCRP inhibitor. Coadministration of Talazoparib with BCRP inhibitors may increase Talazoparib exposure, which may increase the risk of adverse reactions.

USE IN SPECIFIC POPULATIONS
Pregnancy
Based on findings from animal studies and its mechanism of action, Talazoparib can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on Talazoparib use in pregnant women to inform a drug-associated risk. Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus.

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.

Females and Males of Reproductive Potential
Talazoparib can cause fetal harm when administered to pregnant women.

Pregnancy Testing
Pregnancy status should be verifed in females of reproductive potential prior to initiating Talazoparib treatment.

Contraception
Females
Females of reproductive potential should be advised to use effective contraception during treatment and for 7 months following the last dose of Talazoparib.

Males
Based on genotoxicity and animal reproduction studies, male patients with female partners of reproductive potential and pregnant partners should be advised to use effective contraception during treatment with Talazoparib and for 4 months following the last dose.

Infertility
Males
Based on animal studies, Talazoparib may impair fertility in males of reproductive potential.

Pediatric Use
The safety and effectiveness of Talazoparib have not been established in pediatric patients.

Geriatric Use
In clinical trials of Talazoparib enrolling 494 patients with advanced solid tumors who received Talazoparib 1 mg daily as a single agent, 85 (17%) patients were ≥65 years of age, and this included 19 (4%) patients who were ≥75 years old. There were 5 patients ≥85 years old. In the TALAPRO-2 trial, of 197 patients who received Talazoparib, 77% were ≥65 years of age, while 30% were ≥75 years of age. No overall differences in safety or effectiveness of Talazoparib were observed between these patients and younger patients.

Hepatic Impairment
No dosage modification is recommended for patients with hepatic impairment.

Renal Impairment
The recommended dosage of Talazoparib should be reduced in patients with moderate (CLcr 30 – 59 mL/min) and severe (CLcr 15 – 29 mL/min) renal impairment. No dose adjustment is recommended for patients with mild renal impairment (CLcr 60 – 89 mL/min). Talazoparib has not been studied in patients requiring hemodialysis.

PHARMACEUTICAL INFORMATION
Storage Condition
Store below 30°C, in a cool and dry place. Keep away from light and keep out of the reach of children.

HOW SUPPLIED
TALAPARIB capsule: Each HDPE container contains 30 capsules (each capsule contains 1 mg Talazoparib), a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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