Taiwan Food and Drug Administration

Assessment Report

Trade Name：達勝癌膠囊 0.25 毫克/Talzenna Capsules 0.25 mg

Active Ingredient：Talazoparib Tosylate

License Number：MOHW-PI 027801

Applicant：美商惠氏藥廠（亞洲）股份有限公司台灣分公司

Approval Date：2020.02.03

Indication：

TALZENNA 單一療法適用於治療曾接受前導性、術後輔助性或轉移性化療，或無法接受化療，且具生殖細胞 BRCA 1/2 (germline BRCA 1/2)突變併 HER2 陰性之局部晚期或轉移性乳癌成年病人。

TALZENNA monotherapy is indicated for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with chemotherapy in the neoadjuvant, adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments.

1. Background Information

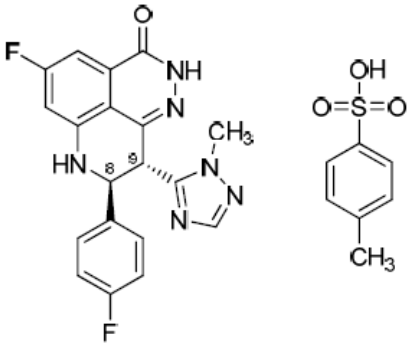
Trade Name	達勝癌膠囊 0.25 毫克 / Talzenna Capsules 0.25 mg
Active Ingredient(s)	Talazoparib Tosylate
Applicant	美商惠氏藥廠（亞洲）股份有限公司台灣分公司
Dosage Form & Strengths	膠囊劑 0.25
Indication	TALZENNA 單一療法適用於治療曾接受前導性、術後輔助性或轉移性化療，或無法接受化療，且具生殖細胞 BRCA 1/2 (germline BRCA 1/2)突變併 HER2 陰性之局部晚期或轉移性乳癌成年病人。 TALZENNA monotherapy is indicated for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with chemotherapy in the neoadjuvant, adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments.
Posology	詳細內容請參閱仿單
Pharmacological Category **ATC Code**	L01XX60

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, talazoparib tosylate, is chemically designated as (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3*H*-pyrido[4,3,2-*de*]phthalazin-3-one 4-methylbenzenesulfonate (1:1) and has the following structure:



It is a white to yellow solid. The molecular formula and the molecular weight of talazoparib tosylate are $C_{26}H_{22}F_2N_6O_4S$ and 552.56 Daltons, respectively. The structure of talazoparib has two asymmetric centers. Talazoparib tosylate is non-hygroscopic.

Adequate information of characterization of the drug substance has been provided. The structure of talazoparib tosylate is confirmed by UV/Vis spectrum, IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, single crystal X-ray diffraction and mass spectrometry. The specification for the drug substance includes tests for appearance, particle size, identification, residual solvents, water content, residue on ignition, organic impurities and assay.

2.1.2 Drug product

Talzenna capsules for oral use contain 0.36 mg of talazoparib tosylate (equivalent to 0.25 mg talazoparib free base). The capsules are packaged in polyvinyl chloride/polyvinylidene chloride (PVC/PVdC) blisters with aluminum peel off foil lidding or high-density polyethylene (HDPE) bottles. The excipients used in the drug product comply with compendial monographs.

The release specification for the drug product includes appearance, identification, assay, degradation products, water content, uniformity of dosage units, dissolution and microbial limits. Analytical methods are described well and validated.

Stability studies of drug product under long term condition (25℃/60% RH and 30℃/75% RH) and accelerated condition (40℃/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Talazoparib is a potent and specific ligand of the α2δ subunit of voltage-dependent Ca^{2+} channels. *In vitro* pharmacology studies demonstrated that talazoparib is a potent and selective inhibitor of PARP1 and PARP2 catalytic activity. Cytotoxicity was observed in various cancer cell lines with gene mutations in DNA damage repair pathways. The cytotoxic

activity of PARP inhibitors has been proposed to be more related to the PARP trapping than directly enzyme inhibition. Talazoparib resulted in increased PARP trapping and was more evident in the BRCA1-mutant cell line, which is sensitive to talazoparib cytotoxicity, than in the less sensitive BRCA1-mutant cell line.

In vivo, talazoparib showed significant antitumor activity in the breast cancer PDX model with or without BRCA mutations. The antitumor efficacy of talazoparib was more potent than carboplatin in a breast cancer PDX model. Talazoparib did not produce significant inhibition of the hERG channel. IC_{50} of hERG inhibition was considered >100 μM and is approximate >6996-fold above the observed unbound human clinical exposure at 1 mg/day human dose.

In vivo, talazoparib showed no significant adverse effects on the cardiovascular system, central nervous system, and respiratory system function.

2.2.2 Toxicological Studies

The repeated-dose toxicity studies were conducted in rats and dogs for up to 13 weeks. The primary talazoparib-related findings by target organ included effects on the hematolymphopoietic system, the male reproductive system, and the gastrointestinal system in both species. Additional findings by target organ involved only the effects in the female reproductive organ and liver in rats. The findings at sub-therapeutic clinical exposure included the hematolymphopoietic, testis, epididymis, and seminiferous tubules toxicities. The decreased reticulocyte, platelet, red blood cell (RBC), and WBC counts may serve as the sensitive and early markers of target organ toxicity. Hematological toxicity needs to be monitored appropriately and managed by dose reduction.

Talazoparib was not mutagenic in a bacterial reverse mutation assay. However, consistent with the genomic instability caused by its pharmacological effect, talazoparib was clastogenic in chromosomal aberration and micronucleus assays. Carcinogenicity studies were not conducted or required to support the use of talazoparib in the proposed indication.

In the embryo-fetal development study in pregnant rats, talazoparib is an embryo-fetal toxicant at a maternal AUC_{24} exposure margin of 0.09-fold (at 0.015 mg/kg/day administered to pregnant dams) to the relevant exposure at the recommended clinical dose of 1 mg/day. Toxicity in the surviving fetuses from dams administered 0.015 mg/kg/day included increased embryo-fetal lethality, embryo/fetal malformations, and structural variations. Based on these results, mechanism of action and genotoxicity, talazoparib is not recommended during pregnancy. Females and males should use effective contraception for 7 and 4 months after the last dose, respectively. Furthermore, mothers should avoid breastfeeding for at least 1 month after the last dose.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following oral administration of talazoparib, the median time to C_{max} was generally between 1 to 2 hours after dosing. After oral administration of 1 mg Talzenna once daily in patients, the geometric mean (CV) of AUC and C_{max} of talazoparib at steady-state was 208 (37%) ng•hr/mL and 16.4 (32%) ng/mL, respectively. The PK of talazoparib is linear from 0.025 mg to 2 mg (2 times of the recommended dose). The median accumulation ratio of talazoparib following repeated oral administration of 1 mg once daily was in the range of 2.3 to 5.2. Talazoparib plasma concentrations reached steady-state within 2 to 3 weeks.

Following a single oral dose of 0.5 mg Talzenna with high-fat, high-calorie food, the mean C_{max} of talazoparib was decreased by 46%, the median T_{max} was delayed from 1 to 4 hours, and AUC_{inf} was not affected.

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. The mean terminal plasma half-life (±SD) of talazoparib is 90 (±58) hours, and the mean apparent oral clearance (inter-subject variability) is 6.45 L/h (31.1%) in cancer patients.

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

Excretion of talazoparib in urine was the major route of elimination. Approximately 68.7% (54.6% unchanged) of the total administered radioactive dose [^{14}C]-talazoparib was recovered in urine, and 19.7% (13.6% unchanged) in feces.

2.3.2 Interaction Studies

In vitro study demonstrated that talazoparib is a substrate of P-gp and BCRP transporters.

In patients with advanced solid tumors, co-administration of a P-gp inhibitor (multiple 100 mg twice-daily doses of itraconazole) with a single 0.5 mg talazoparib dose increased talazoparib AUC_{inf} and C_{max} by approximately 56% and 40%, respectively. Population PK analysis showed that co-administration with P-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil in clinical studies increased talazoparib exposure by 45%. Therefore, reduce the Talzenna dose to 0.75 mg once daily when co-administered with certain P-gp inhibitors.

In patients with advanced solid tumors, co-administration of a P-gp inducer (multiple 600 mg

once-daily doses of rifampin) with a single 1 mg talazoparib dose increased talazoparib C_{max} by 37% with no effect on talazoparib exposure.

The effect of BCRP inhibitors on PK of talazoparib has not been studied. Co-administration with BCRP inhibitors may increase talazoparib exposure.

Co-administration of acid-reducing agents including proton pump inhibitors, histamine receptor 2 antagonists, or other acid reducing agents has no effect on the absorption of talazoparib.

2.3.3 Special Populations

Age (18 to 88 years), sex, race (361 White, 41 Asian, 16 Black, 9 others, and 63 Not Reported), and body weight (36 to 162 kg) had no clinically relevant effect on the PK of talazoparib.

Following multiple oral doses of talazoparib, plasma talazoparib total exposure (AUC_{0-24}) increased by 12%, 43%, and 163% in patients with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function. Talazoparib C_{max} increased by 11%, 32%, and 89% in patients with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function. In addition, a population PK analysis that included 132 patients with mild renal impairment and 33 patients with moderate 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, compared to patients with normal renal function. The PK of talazoparib has not been studied in patients requiring hemodialysis. Considering the risk and benefit, no dose adjustment is recommended for mild renal impairment patients, 0.75 mg once daily for moderate renal impairment patients and 0.5 mg once daily for severe renal impairment patients.

Mild hepatic impairment had no effect on the PK of talazoparib based on population PK analysis. No dose adjustment is recommended in mild hepatic impairment. The PK of talazoparib has not been studied in patients with moderate or severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study 673-301 (also known as C3441009, EMBRACA) was reviewed to evaluate the efficacy of talazoparib over physician’s choice treatment (PCT) in patients with gBRCA-mutated HER2-negative locally advanced or metastatic breast cancer. The primary efficacy endpoint was progression-free survival (PFS), which was assessed by blinded

independent central radiology facility (IRF) review. The key secondary efficacy endpoint was overall survival (OS). To maintain the overall 2-sided type I error rate at 0.05, the PFS and OS analyses were protected under a multiplicity adjustment schema using gate-keeping methodology.

Between October 2013 and April 2017, 431 patients were randomized in a 2:1 ratio to receive talazoparib 1 mg/day (n=287) or 1 of 4 PCTs (n=144) reflecting the standard of care in this disease setting (capecitabine, eribulin, gemcitabine, or vinorelbine).

As of the data cutoff date (15 September 2017), the median PFS by IRF assessment was 8.6 months (95% CI: 7.2, 9.3) in the talazoparib arm compared with 5.6 months (95% CI: 4.2, 6.7) in the PCT arm (HR=0.54 [95% CI: 0.41, 0.71]; $p < 0.0001$). Results of the investigator-assessed PFS analysis (HR: 0.538; 95% CI: 0.42, 0.69; $p < 0.0001$) also supported the primary PFS by IRF analysis.

In the interim OS analysis, median OS was 22.3 months (95% CI: 18.1, 26.2) in the talazoparib arm and 19.5 months (95% CI: 16.3, 22.4) in the PCT arm (HR=0.76 [95% CI: 0.547, 1.060]; $p = 0.1053$). The expected number of deaths for final analysis of OS has not been observed yet.

The subgroup analyses were generally in keeping with the primary analysis. In Study 673-301, initially, about 40% of subjects with hormone receptor positive had received previous hormone therapy. The limited data showed no obvious difference in PFS or objective response rate for those who received hormone therapy or not.

In summary, in the pivotal randomized Phase 3 Study 673-301, talazoparib demonstrated a statistically significant improvement in PFS over PCT in patients with gBRCA-mutated HER2-negative locally advanced or metastatic breast cancer.

2.4.2 Safety Results

The safety profile of talazoparib treatment was similar to other PARP inhibitors. The most common adverse events (AEs) in talazoparib were fatigue, anemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhea, constipation, decreased appetite, and back pain. Anemia occurred more frequently in talazoparib group than PCT group (52% vs. 18%). In talazoparib arm, the incidence of Gr 2 and Gr 3 anemia were 10% and 38%. Other myelosuppression related AEs that occurred more than 5 % in talazoparib arm included neutropenia (27%), thrombocytopenia (16%), platelet count decreased (12%), neutrophil count decreased (10%), WBC count decreased (9%), leukopenia (8%).

In the pivotal study 673-301, there were no confirmed cases of MDS, while one subject (0.8%) had AML in the PCT group. In the pooled studies of patients receiving talazoparib 1 mg/day there were no reports of AML, leukemia was reported for a patient who received a starting dose of talazoparib at 0.5 mg/day. Subsequent to the initial clinical database snapshot, AML was reported in 1 patient in the talazoparib arm, which developed after the end of the safety reporting period (>30 days from last dose).Overall, MDS/AML has been reported in 2 out 584 (0.3%) solid tumor patients treated with single agent talazoparib.

In summary, talazoparib showed an acceptable safety profile in patients with gBRCA-mutated HER2-negative locally advanced or metastatic breast cancer.

2.5 Bridging Study Evaluation

In population PK analysis, the mean CL/F of Asian (N=41；8% in overall) was shown to be 28.1% higher than that of non-Asian patients which is corresponding to a 19.2% lower exposure (AUC) in Asian patients. The inter-subject variation was about 32~37% after oral administration and no CYP450 enzyme was involved drug metabolized. Considering the inter-subject variation and metabolism of talazoparib, talazoparib is considered none to minimally ethnically sensitive between Asian and Caucasian from the PK aspect.

Although a low proportion of Asian population was involved in population PK analysis, the preliminary result from Japanese phase I dose escalation study (Study C3441030) recommended 1 mg QD as the RP2D, the same as Caucasian proposed posology.

The sponsor provided East Asian data of 33 subjects from the global pivotal trial Study 673-301(accounting for 8% overall population). The East Asian data was from Taiwan and Korea. The efficacy (including PFS, OS and DOR) and safety profile in the East Asian were generally comparable with the global data. The OS data in overall population is immature but with positive trend.

In summary, the ethnic difference in this application is not significant. Bridging studies could be waived.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy of talazoparib was demonstrated by superiority to physician’s choice treatment (PCT) in PFS in patients with gBRCA-mutated HER2-negative locally advanced or metastatic breast cancer in an open-label, randomized, controlled study. The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post market setting. A risk management plan (RMP) is not required

to ensure that the benefits of the drug outweigh the risks.

The regular approval of talazoparib is recommended, for the indication as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with chemotherapy in the neoadjuvant, adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments.

3. Post-Marketing Requirements

The applicant should provide the final OS analysis of study 673-301.
The applicant should provide the final study report of Study C3441002.