Taiwan Food and Drug Administration

Assessment Report

Trade Name： Zejula Capsules

Active Ingredient：Niraparib

License Number：MOHW-PI 027764

Applicant：台灣武田藥品工業股份有限公司

Approval Date：2020/01/13

Indication：用於對含鉑化療有完全或部分反應的復發性表皮卵巢癌、輸卵管腫瘤或原發性腹膜癌成年病人之維持治療。病人須對復發前含鉑化療有敏感性

Zejula is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Patients must be platinum-sensitive before relapsed.

Background Information

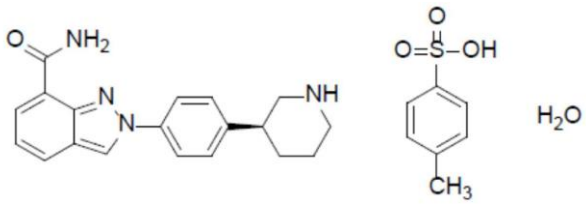
Trade Name	Zejula Capsules
Active Ingredient(s)	niraparib
Applicant	Takeda Pharmaceutical Company Limited
Dosage Form & Strengths	Capsule 100 mg
Indication	Zejula is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Patients must be platinum-sensitive before relapsed.
Posology	The recommended dose is three 100 mg hard capsules once daily, equivalent to a total daily dose of 300 mg.
Pharmacological Category **ATC Code**	L01XX54

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, niraparib tosylate monohydrate, is chemically designated as 2-{4-[(3*S*)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide 4-methyl benzenesulfonate hydrate (1:1:1) and has the following structure:



It is a white to pale brown powder. The molecular formula and the molecular weight are $C_{19}H_{20}N_4O \cdot C_7H_8O_3S \cdot H_2O$ and 510.61, respectively. It is non-hygroscopic. The structure of niraparib tosylate monohydrate is confirmed

by UV, IR spectrum, mass spectrum, nuclear magnetic resonance spectrum, elemental analysis, and single crystal X-ray crystallography.

The specification of drug substance includes tests for description, identification, impurities, water content, particle size, and assay.

2.1.2 Drug product

The strength of Zejula® Capsules is 100 mg of niraparib (equivalent to 159.4 mg of niraparib tosylate monohydrate). The excipients used in the drug product comply with the compendial monographs.

Specifications have been presented for Zejula® Capsules and the test items include description, identification, impurities, uniformity of dosage units, water content, dissolution, microbial enumeration, and assay. Analytical methods are described and validated.

Stability studies of drug product under long term condition (25°C/60% RH) and accelerated condition (40°C/75% RH) have been performed.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Niraparib is at least 100-fold more selective for poly (ADP-ribose) polymerase (PARP) -1/-2 than other catalytically active PARP family members. The primary circulating metabolite of niraparib in rats and dogs, M1, did not inhibit PARP-1 or PARP-2 *in vitro*. Niraparib showed 25- to 160-fold selectivity in proliferation assays against cancer cell lines where BRCA1/2 expression was knocked down. Niraparib also showed inhibition in *BRCA* mutant cell lines compared to their wild-type counterparts. In addition, niraparib had ≥13-fold selectivity margin when comparing the average *BRCA*mut tumor cell CC_{50} to normal hematopoietic cells.

Niraparib is well tolerated and efficacious in *BRCA1*mut MDA-MB-436 (breast cancer cell line) xenograft models. Niraparib inhibited tumor growth to 36 % of baseline on *BRCA2*mut (PH077) and regressed to within 8 % of baseline on *BRCA*wt, HRDpos (PH039) in patient derived xenograft models of high-grade serous ovarian cancer. PARP inhibition was also confirmed after oral administration to mice in murine PBMCs and implanted xenograft tumors. In

addition, niraparib maintenance therapy after tumor response to chemotherapeutic agents may prolong recurrence-free survival.

Off-target activity of niraparib was shown to inhibit the uptake of dopamine and norepinephrine. However, niraparib treatment did not result in behavioral or neurochemical effects in mice at plasma levels which had been shown to cause anti-tumor activity *in vivo*. In safety pharmacology, dose-related increases in heart rate and mean arterial pressure were observed, but no effects on neurological function and on the respiratory system.

2.2.2 Toxicological Studies

The findings observed in the repeated-dose toxicity studies showed dose -dependence in both rat and dog, as well as consistency and reproducibility between species and across studies. Since the bone marrow is the main target organ for toxicity, subsequent reduction in RBC and WBC parameters and lymphoid depletion in the bone marrow, spleen, thymus and lymph nodes were observed. In the one-month rat study, infections and septicemia observed are considered secondary to the lymphoid depletion, leading to mortality in male rats.

The testis was also identified as a target organ for toxicity in rat and dog, and the effects were seen as testicular germ cell depletion, decreased amount of spermatogenic epithelium and testicular hypospermatogenesis in the three-month rat study, the one-month and the three-month dog studies, respectively. All findings were partially or complete reversible. Niraparib is expected to be embryo-fetal toxic based on its mechanism of action. Niraparib is considered clastogenic, as expected from its pharmacologic action. There was no evidence of cutaneous or ocular phototoxicity of niraparib.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

All the clinical PK trials of niraparib were conducted only in oncology patients. Niraparib was rapidly absorbed with mean C_{max} peaked at about 4 hour after oral administration. The absolute bioavailability of niraparib is determined to be approximately 73%. No clinically impactful food effect was observed. Niraparib exhibited a linear PK and time-invariant properties at dose levels from 30 to 400 mg administered once daily. The accumulation ratio is 2.4 at the clinical

dose following repeated daily dosing.

Niraparib exhibits concentration-independent binding to human plasma proteins with fraction unbound of 0.17. The apparent V_d/F was 1074 L estimated by population PK analysis. In humans, niraparib is primarily metabolized by carboxylesterases forming the inactive metabolite M1. M1 is subsequently glucuronidated by UGTs to form M10. The average steady state terminal half-life was about 36 hours. Overall, the amount of radioactive niraparib-derived materials excreted in urine and feces accounted for 47.5% (11% as unchanged niraparib) and 38.8% (19% as unchanged niraparib) of the administered dose, respectively.

2.3.2 Interaction Studies

The potential for clinically relevant drug-drug interactions with niraparib is considered low. *In vitro*, niraparib is a BCRP and P-gp substrate. Both of niraparib and its primary metabolite are not a substrate, inhibitor, or inducer of CYP450 enzymes at clinically relevant concentrations. Niraparib inhibits BCRP at an IC_{50} value of 1.21 μg/mL, but the unbound steady state concentration at the clinical dose is below the IC_{50} value for BCRP.

2.3.3 Special Populations

Pop PK analysis suggested that there are no difference in the exposure among patients with mild, moderate renal impairment and normal renal function. Similar results were noted between patients with normal hepatic function and those with mild hepatic impairment. Therefore, no starting dose adjustment is needed in patients with mild to moderate renal impairment or patients with mild hepatic impairment. There is no sufficient information to adequately characterize the PK and safety of niraparib in patients with moderate or severe hepatic impairment and in patients with severe renal impairment or end-stage renal disease undergoing hemodialysis.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

There is one phase III pivotal study (NOVA study) to demonstrate the efficacy and safety of niraparib in patients with maintenance therapy for recurrent platinum-sensitive ovarian cancer. NOVA study was a phase III, randomized, double-blind, placebo-controlled study. Eligible patients were separated into

two cohorts and were evaluated independently: (1) germline BRCA mutation (gBRCAmut cohort), and (2) no germline BRCA mutation but with high-grade serous or high-grade predominantly serous histology (non-gBRCAmut cohort). In each cohort, enrolled subjects underwent 2:1 randomization to niraparib or placebo arm, stratified by time to progression after the penultimate platinum therapy, use of bevacizumab, and best response during the last platinum regimen. The dose of niraparib was 300mg daily until disease progression or unacceptable toxicities. The primary endpoint was progression-free survival via independent blinded central review. The two cohorts were independently powered to test for the superiority of niraparib versus placebo. In the non-gBRCAmut cohort, the primary analysis was performed in a hierarchical manner, with test in the homologous recombination deficiency (HRD) positive group performed first, followed by a test of the overall non-gBRCAmut cohort if the test on the HRD positive group was statistically significant.

Niraparib met the primary endpoint of prolonging PFS compared with placebo in all three primary patient populations (gBRCAmut cohort, HRD positive group of the non-gBRCAmut cohort, and the overall non-gBRCAmut cohort). In the gBRCAmut cohort, patients in the niraparib arm achieved a median PFS of 21.0 months, significantly longer than that in placebo group of 5.5 months ($p<0.0001$) with a hazard ratio of 0.26 (95% CI: 0.17, 0.41). In the non-gBRCAmut cohort, patients with HRD positive tumors in the niraparib arm achieved a median PFS of 12.9 months, significantly longer than that in placebo group of 3.8 months ($p<0.0001$) with a hazard ratio of 0.38 (95% CI: 0.24, 0.59). In the overall non-gBRCAmut cohort, patients in the niraparib arm achieved a median PFS of 9.3 months, significantly longer than that in placebo group of 3.9 months ($p<0.0001$) with a hazard ratio of 0.45 (95% CI: 0.34, 0.61).

2.4.2 Safety Results

In NOVA study, the most common AEs (>20%) were nausea, anemia, thrombocytopenia, fatigue, constipation, vomiting, headache, decreased appetite, insomnia, abdominal pain and platelet count decreased. The proportion of Grade 3/4 AEs and AEs leading to dose reduction were higher in subjects receiving niraparib than placebo (Gr 3/4 AE: 74.1% in niraparib and 22.9% in placebo; AE leading to dose reduction: 68.9% in niraparib and 5.0% in placebo). The most common reasons for dose reduction were thrombocytopenia and anemia. Among Grade 3/4 AEs, thrombocytopenia,

anemia, neutropenia, hypertension, and fatigue were common and the incidence of these Grade 3/4 AEs was higher than that in the placebo group.

Among subjects receiving niraparib in NOVA study, 61.3%, 50.1%, and 35.1% subjects developed thrombocytopenia event, anemia event, and leukopenia event; 40.3%, 18.5%, and 9.5% subjects had dose reduction due to the accordant events. Dose-response relationship was observed for the occurrence of high grade thrombocytopenia, highest with niraparib 300mg dose. Most of the hematological adverse events occurred in the first one or two months after treatment, and most of the events could be managed by dose reduction and transfusion therapy. The concurrent bleeding events with thrombocytopenia were generally mild in severity.

In the NOVA study, the incidence of MDS/AML is 1.4% in the niraparib arm and 1.1% in the placebo arm. Most of the subjects (5/7) developing MDS/AML had received three or more prior lines of chemotherapy. Fatal outcome has been noted for subjects with MDS/AML. Overall, across all niraparib treated subjects in the clinical program, the incidence of MDS/AML with niraparib treatment was 0.9%, which is similar with the incidence of MDS/AML among ovarian cancer patients.

The sponsor proposed a lower starting dose instead of 300mg used in the NOVA trial. The evidence was based on a post-hoc analysis showing that the incidence of thrombocytopenia was higher among subjects with weight<77kg or baseline platelet<150,000/uL (34.6% vs. 11.8%). However, this analysis did not adjust influential factors other than body weight. Besides, the pop PK study showed no obvious effect on PK profile by body weight. Considering that 1.niraparib therapy is for the treatment of a life threatening disease and most of the thrombocytopenia events are manageable. 2. The safety information of initial lower dosage is insufficient and the efficacy evidence of the reduced dosage is absent. We recommend 300mg as the appropriate starting dose of, with clear instruction for dosage adjustment and monitoring procedure in the labeling.

2.5 Bridging Study Evaluation

The impact of ethnic factors on niraparib PK was evaluated by cross-study comparison. PK exposures between Japanese and Caucasian cancer patients

from two separately intensive PK studies were compared. The results showed that AUC_{24hr}, C_{max} and C_{24hr} in Japanese patients were 20% to 25% lower to Caucasian patients at the clinical dose of 300 mg following single or repeated daily dosing. Overall, there appeared to be no significant ethnic difference in PK between the Japanese and Caucasian subjects.

The clinical bridging data mainly came from Japanese study Niraparib-2001. Niraparib-2001 was a phase 2, multicenter, open-label, single–arm study to evaluate the safety of niraparib in Japanese patients with platinum-sensitive, relapsed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, who had response to the last platinum-based chemotherapy. All subjects received 300 mg of niraparib as starting dose. A total of 19 subjects were enrolled. Up to data cutoff, there was no PFS event, and all subjects were alive. Overall, the safety results of Japanese subjects were considered generally comparable to global subjects in pivotal NOVA study. The incidence of myelosuppression including thrombocytopenia, anemia, and leukopenia was comparable between Japanese subjects and subjects in NOVA study. .

Based on the above evidence, we recommended conditional waiver of the bridging study of niraparib. Final analysis of Niraparib-2001 should be submitted when available.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy of niraparib was demonstrated by superiority to placebo in PFS for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. 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.

In conclusion, the overall benefit/risk ratio is favorable to support approval of the claimed indications.

3. Post-Marketing Requirements

1. The sponsor should provide the final CSR of NOVA study after its completion.
2. The sponsor should provide the final CSR of study Niraparib-2001 after its completion.