Taiwan Food and Drug Administration

Assessment Report

Trade Name： Jevtana Concentrate and solvent for solution for infusion

Active Ingredient： CABAZITAXEL

License Number： DOH-PI 025633

Applicant： Sanofi Taiwan Co., Ltd

Approval Date： 101/02/28

Indication： Cabazitaxel (Jevtana) is indicated in combination with prednisone/prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

1. Background Information

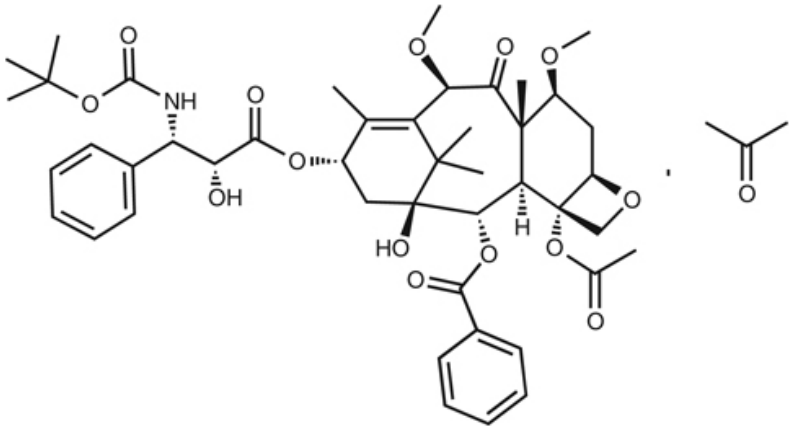
Trade Name	Jevtana Concentrate and solvent for solution for infusion
Active Ingredient(s)	**CABAZITAXEL**
Applicant	**Sanofi Taiwan Co., Ltd**
Dosage Form & Strengths	Injection/ each vial contains 60mg
Indication	**Cabazitaxel (Jevtana) is indicated in combination with prednisone/prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.**
Posology	N/A
Pharmacological Category **ATC Code**	

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The active substance, cabazitaxel, is chemically designated as (2α,5β,7β,10β,13α)-4-(acetoxy)-13-({(2R,3S)-3-[(tertbutoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5, 20-epoxytax-11-en-2-yl benzoate. It is presented with a stoichiometric molecule of acetone as the solvate in the solid state. The structure is shown below:



It is a white to almost white crystalline powder. The molecular formula is $C_{45}H_{57}NO_{14} \cdot C_3H_6O$ and molecular weight is 894.01 (acetone solvate). The structure has 11 chiral centers. The specific stereochemistry is presented and no stereoisomer occurs. Cabazitaxel shows polymorphism and form A is selected.

Adequate information on characterization of the drug substance has been provided. The structure of cabazitaxel is confirmed by UV, IR, mass spectrometry,

nuclear magnetic resonance spectrum (^{1}H-NMR, ^{13}C-NMR) and single crystal X-ray diffraction. The spectrum assignations were consistent with the declared chemical structure.

The specification includes tests for appearance, color and clarity of solution, identity, specific optical rotation, acetone content, assay, related substances, residual solvents, heavy metals, water content, sulphated ash, microbial limit and bacterial endotoxins. A rationale of the acceptance criteria is provided and based on analytical data from the release and stability studies of drug substance batches manufactured during development, and toxicological safety assessment.

2.1.2 Drug product

The drug product Jevtana® Injection is supplied as a kit consisting of the non-aqueous concentrate, cabazitaxel (anhydrous and solvent free) 60 mg/1.5 mL for solution for infusion, and the diluent, 5.67 mL of a 13%w/w aqueous alcohol for dilution. The diluent is used for preparation of an intermediate premix at 10 mg/ml prior to dilution with 0.9% sodium chloride solution or 5% dextrose solution in the infusion bag.

The excipients used in the concentrate are complied with the compendial monographs or in-house specifications. The excipient is of vegetable origin. During the development of Jevtana® Injection, compatibility, manufacturing process and microbiological attributes were studied and established. A robust process is further confirmed by three consecutive batches of process validation.

Adequate release and shelf-life specification have been presented for the Jevtana® Injection and test items include description, identification, assay, degradation products, uniformity of dosage units, pH, water content, sterility and bacterial endotoxin. The results of batch analysis are all complied with the specification. For non-pharmacopoeia methods, validations are performed and accepted in terms of specificity, linearity, accuracy, repeatability, intermediate precision and LOD/LOQ.

For the concentrate for solution for infusion and the solvent for dilution, stability studies under long-term (5°C, 25°C/60% RH and 30°C/65% RH) and accelerated (40°C/75% RH) conditions have been carried out on three commercial-scale batches. The products are packaged in the container closure system intended for marketing. The parameters evaluated during the stability study are appearance, color, assay, degradation products, water content, particular contamination, sterility, bacterial endotoxins and container closure integrity. Since up to 12 months of 30°C/65% RH long-term and 6 months of accelerated stability data showed no significant changes, the stability study under 25°C/60% RH is discontinued. Precipitates have been observed from three

batches stored at 5°C. Therefore, it is not recommended to refrigerate the drug product during storage. The shelf life of Jevtana® injection can be tentatively granted for 24 months under the storage condition of 30°C. In addition, the stability of infusion (diluted with 0.9% sodium chloride solution or 5% dextrose solution) has been demonstrated for 8 hours at ambient temperature.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Jevtana Injection (60 mg cabazitaxel /1.5 mL) is a microtubule inhibitor indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer (HRPC) previously treated with a docetaxel-containing treatment regimen. Jevtana (25 mg/m^2) administered every three weeks as a one-hour intravenous infusion in combination with oral prednisone 10 mg administered daily throughout Jevtana treatment.

In vitro pharmacological studies demonstrate that cabazitaxel is as potent as docetaxel against docetaxel-sensitive tumor cell lines. In addition, cabazitaxel has a better antiproliferative activity on resistant cell lines than docetaxel. *In vivo* pharmacological studies show that cabazitaxel is as potent as docetaxel against docetaxel-sensitive tumors including murine tumors and human tumors.

In safety pharmacological studies, administration of cabazitaxel produced similar cardiovascular hemodynamic and respiratory changes similar to those noted after the administration of the vehicle alone (PS80/ethanol/5% glucose) in anesthetized dogs and were therefore likely attributable to the PS80 component of the vehicle (non-specific histamine releaser in dogs). The results of the nonclinical safety studies suggest that the principal adverse effects of cabazitaxel are consistent with the pharmacological (antimitotic) activity of a taxoid-type antineoplastic compound and resemble those reported for other taxoid anticancer drugs (docetaxel, paclitaxel). No physiologically relevant effects were noted in the central nervous, respiratory and gastro-intestinal systems after intravenous administration of cabazitaxel in rats. Treatment with microtubule- stabilizing drugs is often associated with neurotoxicity (observed with paclitaxel and docetaxel) a potentially severe side effect limiting the clinical use of these agents.

2.2.2 Toxicological Studies

In single-dose neurotoxicity studies, administration of cabazitaxel in mice also produced central and peripheral neurotoxicity. Microscopic findings were observed in organs with high cell turnover as the bone marrow (cellular depletion), the lymphoid systems (atrophy and/or increased lymphocytolysis), the gastrointestinal tract (epithelial cell necrosis and/or cell degeneration/regeneration) and the male reproductive system (atrophy, cell necrosis

and/or regeneration). In a few instances, effects on organs with lower epithelial tissue turnover were noted. In particular, increased numbers of mitotic figures or single cell necrosis were observed in the liver, adrenal gland, uterus and eyes. In the multiple-cycle toxicity study in the rat, compound-related findings were observed the skin (alopecia). The effects on the skin could be correlated with alopecia observed in few instances in human. Most of the changes in general toxicity studies were reversible within the duration of the recovery periods and were considered compatible with a treatment every 3 weeks. Effects in skin and male reproductive organs should be reversible with a longer duration of recovery period. In the multiple-cycle toxicity study in the rat, compound-related findings were observed in the teeth (ameloblast atrophy). These effects in teeth were not reversible during the 28 days observation. However, they were not considered relevant for human as this finding is due to the fact that rat teeth are open-rooted which means they grow throughout rat life. Cabazitaxel was found negative in the bacterial reverse mutation test (Ames test). The effects observed in the *in vitro* chromosome aberration test (increased number of polyploid cells) and the increased incidence of micronucleated polychromatic erythrocytes noted in the *in vivo* bone marrow micronucleus test were consistent with the pharmacological activity of the compound (inhibition of tubulin depolymerization) and were observed with other compounds with the same pharmacological activity. Cabazitaxel induced embryo-fetal toxicity in rats, linked with maternal toxicity and consisting of fetal deaths and decreased mean fetal weight associated with delay in skeletal ossification. Similar findings have been reported with docetaxel or paclitaxel. Cabazitaxel did not induce fetal abnormalities in rats and rabbits and did not affect mating performances or fertility of male and female rats. Cabazitaxel did not show an irritation potential in a local intravenous, paravenous or intra-arterial tolerance study conducted in rabbits and was found compatible with human plasma, serum and blood *in vitro* up to a concentration of 0.5 mg/mL.

In conclusion, the embryo-fetal toxicities should be described on the labeling. The technical data submitted by sponsor is acceptable. This NDA is recommended to be approved from the preclinical pharmacological and toxicological point of view.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Based on the popPK analysis, t_{max} was reached at the end of one-hour infusion. AUC and C_{max} were dose proportional in the range of 10 to 30 mg/m^2 in patients with advanced solid tumors. The volume of distribution was high, 4,864 L at steady state. *In-vitro*, the binding of cabazitaxel to human serum proteins was 89-92%. The *in-vitro* blood to plasma concentration ratio in human blood ranged from 0.9-0.99, indicating that cabazitaxel was equally distributed between blood and plasma. Cabazitaxel is extensively metabolized in the liver,

mainly by the CYP3A4/5 isoenzyme, and to a lesser extent by CYP2C8. Cabazitaxel is the main circulating moiety in human plasma. Seven metabolites were detected in plasma, and the main metabolite is RPR123142. Cabazitaxel is mainly excreted in the feces as numerous metabolites (76% of the dose); while renal excretion of cabazitaxel and metabolites accounted for 3.7% of the dose (2.3% as unchanged drug in urine). Cabazitaxel can be described by a three-compartment pharmacokinetic model with a terminal half-life of 95 hr.

2.3.2 Interaction Studies

Cabazitaxel is a substrate for P-gp but not for MRP1, MRP2 or BCRP. According to the I/IC_{50} values, the potential for cabazitaxel to inhibit MRPs, P-gp or BCRP substrate is unlikely. *In-vitro* study demonstrated that the risk of interaction due to inhibition of CYP enzymes by cabazitaxel is unlikely with CYP1A2, 2B6, 2E1, 2C8, 2C9, 2C19, and 2D6, but the I/Ki value was above 0.1 for CYP3A. No formal studies regarding strong CYP3A inhibitor/inducer on cabazitaxel have been conducted. Some information should be described in the labeling as follows.

1) *In-vitro* study demonstrated that cabazitaxel had inhibitory effect on CYP3A, indicating a possible risk of interaction with CYP3A substrates *in-vivo*. The *in-vivo* effect of cabazitaxel on CYP3A substrates is unknown. Caution should be exercised when co-administer cabazitaxel with CYP3A substrates given that the exposures of CYP3A substrates may be increased.

2) *In-vitro* study demonstrated that cabazitaxel is a substrate for P-gp, indicating a possible risk of interaction with P-gp inhibitors *in-vivo*. The *in-vivo* effect of P-gp inhibitors on cabazitaxel is unknown. Caution should be exercised when co-administer cabazitaxel with P-gp inhibitors given that the exposures of cabazitaxel may be increased.

2.3.3 Special Populations

No formal studies regarding patients with renal impairment and hepatic impairment have been conducted. A population PK analysis in 170 subjects, creatinine clearance is not a significant covariate. Since there was no data on severe and end-stage renal impairment patients, cabazitaxel should be used with caution in patients with renal impairment. Because of highly metabolism of cabazitaxel, patients with hepatic impairment may have higher systemic exposure.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Cabazitaxel (Jevtana) is indicated in combination with prednisone/prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen. The sponsor provided one Phase III, active-controlled study (Study EFC6193) to support the efficacy of cabazitaxel. All eligible patients were randomly assigned (1:1) to receive mitoxantrone plus prednisone or cabazitaxel plus prednisone every 3 weeks. Randomization was stratified by measurability of disease

(measurable versus non-measurable disease) and ECOG performance status (0 or 1 versus 2). A dynamic allocation method was used to avoid extreme imbalance of treatment assignment within a center.

The primary endpoint was overall survival (OS) defined as the time from the date of randomization to the date of death due to any cause. The secondary endpoints included progression free survival (PFS), time to tumor progression, time to PSA (prostate specific antigen) progression, time to pain progression, and overall tumor response. PFS was defined as the time between randomization and the date of progression or death due to any cause, where a progression was either PSA progression, a tumor progression, or a pain progression. The intent-to-treat (ITT) population was the primary population which included all randomized patients. The OS and PFS were analyzed by log rank test stratified by stratification factors. There were two interim analyses. The first interim analysis for futility was performed after 225 PFS events were collected. The second interim analysis for efficacy was performed when 365 deaths (71.4% of the 511 deaths in the final analysis of the protocol) occurred using the O'Brien-Fleming spending function adjusting for type I error. Thus, significance level for this interim analysis was 0.0160, and that for the final analysis was 0.0452.

In the second interim analysis for efficacy, the cabazitaxel treatment group was statistically superior to the mitoxantrone treatment group in prolonging overall survival time (HR=0.72, 95% CI: 0.57 to 0.90) with p-value of 0.0036 less than the predefined level of significance for interim analysis (p=0.016). However, IDMC recommended that the trial should continue to the final analysis. The analytical results of the final analysis are presented in Table 1. Cabazitaxel plus prednisone treatment significantly prolonged the overall survival time compared to mitoxantrone plus prednisone treatment (HR=0.70, 95% CI: 0.59 to 0.83; p<0.0001). The superiority of cabazitaxel over mitoxantrone in overall survival was consistently demonstrated in subgroup analyses. In addition, the cabazitaxel plus prednisone treatment was also superior to mitoxantrone plus prednisone treatment in progression free survival (HR=0.74, 95% CI: 0.64 to 0.86; p<0.0001), time to tumor progression (HR=0.61, 95% CI: 0.49 to 0.76; p<0.0001) and time to PSA progression (HR=0.75, 95% CI: 0.63 to 0.90; p=0.001), as well as tumor response rate (14.4% versus 4.4%; p=0.0005).

Table 1 Summary results of the final analysis

	mitoxantrone + prednisone n=377	cabazitaxel + prednisone n=378
Overall survival (primary endpoint)		
No. of events	279 (74.0%)	234 (61.9%)
Median (months)	12.7	15.1
Hazard ratio (95%CI)		0.70 (0.59, 0.83)
p-value (stratified log-rank test)		**<0.0001**

Progression free survival		
No. of events	367 (97.3%)	364 (96.3%)
Median (months)	1.4	2.8
Hazard ratio (95%CI)		0.74 (0.64, 0.86)
p-value (stratified log-rank test)		**<0.0001**
Time to tumor progression		
No. of events	180 (47.7%)	170 (45.0%)
Median (months)	5.4	8.8
Hazard ratio (95%CI)		0.61 (0.49, 0.76)
p-value (stratified log-rank test)		**<0.0001**
Time to PSA progression		
No. of events	252 (66.8%)	252 (66.7%)
Median (months)	3.1	6.4
Hazard ratio (95%CI)		0.75 (0.63, 0.90)
p-value (stratified log-rank test)		**0.001**
Time to pain progression		
No. of events	98 (26.0%)	113 (29.9%)
Median (months)	Not reached	11.1
Hazard ratio (95%CI)		0.91 (0.69, 1.19)
p-value (stratified log-rank test)		0.5192
Overall tumor response rate		
Response rate	4.4%	14.4%
P-value (Chi-square test)		**0.0005**

In summary, there is sufficient evidence to support the efficacy of cabazitaxel for the claimed indication.

2.4.2 Safety Results

Main adverse events include neutropenia (94%), febrile neutropenia (7.5%), infections, anemia (98%), thrombocytopenia (48%), hypersensitivity reaction, nausea (34%), vomiting (22%), diarrhea (47%), renal failure, fatigue (37%), constipation (20%), asthenia (20%), abdominal pain (17%), hematuria (17%), anorexia (16%), peripheral neuropathy (13%), dyspnea (12%), dysguesia (11%), cough (11%) and alopecia (10%). G-CSF may be administered to reduce the risks of neutropenia.

2.5 Bridging Study Evaluation

Cabazitaxel is administered by IV infusion. Cabazitaxel has a linear PK profile in the dose range from 10 to 30 mg/m^2 in patients with advanced solid tumors. It is a drug with narrow therapeutic range and not a pro-drug. Due to its route of administration, there was no food effect concern. CYP3A contributes for majority of hepatic clearance. The remaining contribution could be attributes to CYP2C8. CYP3A and CYP2C8 are enzymes known to have genetic polymorphism, however, the clinical impact on cabazitaxel is unknown. There was a population PK study to compare the PK of Caucasian and Oriental populations. However, the sample size of East Asian patients is limited. Considering its pharmacokinetic characteristics and unmet medical needs, intrinsic factors may not be an issue for cabazitaxel from PK perspective.

Thirty-five Asian subjects, 5% of overall study population, were enrolled in the pivotal study EFC6193; subgroup analysis of Asian population revealed a hazard ratio of 0.61 (95% CI: 0.25, 1.45) for the primary endpoint overall survival. The SAEs of carbazitaxel are 52.9% for Asian subgroup and 39.1% for overall population; contrarily, SAEs of comparator (mitoxantrone) are 11.1% for Asian subgroup and 20.8% for overall population. Ethnic difference could not be concluded due to small sample sizes in Asian.

Bridging study was waived because it is a second-line treatment for hormone refractory metastatic prostatic cancer for which no therapy is available currently. The sponsor should conduct a phase IV study, focusing on clinical safety, in this country. Post-marketing of safety data collection is warranted, especially for neutropenia and diarrhea.

2.6 Conclusion

A single pivotal study of carbazitaxel demonstrated overall survival benefit in interim analysis with hazard ration 0.72 as compared to mitoxantrone. Major adverse events included hematological toxicities, infection, renal failure, gastrointestinal symptoms, and peripheral neuropathy. The benefit outweighs the risks.

3. Post-Marketing Requirements

The sponsor should conduct a phase IV safety study to collect more safety information in this country; routine post-marketing safety surveillance should emphasize on neutropenia and diarrhea.