Taiwan Food and Drug Administration

Assessment Report

Trade Name：NUBEQA F.C. Tablets 300 mg

Active Ingredient：Darolutamide

License Number：MOHW PI 027936

Applicant：BAYER TAIWAN COMPANY LTD.

Approval Date：2020/11/03

Indication ： NUBEQA is indicated for the treatment of non-metastatic castration resistant prostate cancer (nmCRPC).

Background Information

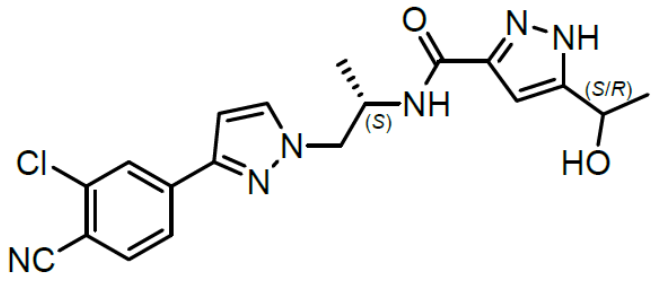
Trade Name	NUBEQA F.C. Tablets 300 mg
Active Ingredient(s)	Darolutamide
Applicant	BAYER TAIWAN COMPANY LTD.
Dosage Form & Strengths	Film-coated tablets 300.0 mg
Indication	NUBEQA is indicated for the treatment of non-metastatic castration resistant prostate cancer (nmCRPC). 適用於治療非轉移性的去勢抗性前列腺癌(nmCRPC)病人
Posology	The recommended dose is 600 mg darolutamide taken twice daily, equivalent to a total daily dose of 1200 mg. The tablets should be taken whole with food. 建議劑量為每日服用兩次 600mg darolutamide，每日總劑量相當於 1200 mg。 建議與食物併服並吞服整顆藥錠。
Pharmacological Category **ATC Code**	L02BB06

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, darolutamide, is chemically designated as *N*-{(2*S*)-1-[3-(3-chloro-4-cyanophenyl)-1*H*-pyrazol-1-yl]propan-2-yl}-5-(1-hydroxyethyl)-1*H*-pyrazole-3-carboxamide and has the following structure:



It is a white to greyish- or yellowish-white powder. The molecular formula and the molecular weight are $C_{19}H_{19}ClN_6O_2$ and 398.85 g/mol, respectively. It is non-hygroscopic. The structure of darolutamide is confirmed by IR spectrum, Raman spectrum, mass spectrum, nuclear magnetic resonance spectrum, and UV/VIS.

The specification of drug substance includes tests for appearance, identification, assay, diastereomeric ratio, loss on drying, microbiological impurities, and impurities.

2.1.2 Drug product

NUBEQA F.C. Tablets 300 mg for oral use contains 300 mg of darolutamide. The excipients used in the drug product comply with the compendial monographs.

Specifications have been presented for NUBEQA F.C. Tablets 300 mg and the test items include appearance, identity, assay, uniformity of dosage units, degradation products, dissolution, and microbial purity. Analytical methods are described 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 performed.

2.2 Preclinical Pharmacology/Toxicology Evaluation

The active ingredient of NUBEQA is darolutamide, a 1:1 mixture of the two diastereoisomers (*S*,*R*)-darolutamide and (*S*,*S*)-darolutamide.

2.2.1 Pharmacological Studies

Darolutamide and its metabolite keto-darolutamide potently bound to androgen receptor (AR), inhibited the transactivation of wildtype and mutated AR, and inhibited cell proliferation of an androgen-sensitive cell line. Darolutamide showed antitumor activity in multiple rodent disease models. Effects of darolutamide, (*S*,*R*)-darolutamide, (*S*,*S*)-darolutamide, and keto-darolutamide on a panel of over 100 targets, did not show off-target activity in vitro at concentrations achieved in humans following oral dosing with 600 mg of darolutamide twice daily. Darolutamide and keto-darolutamide functioned as a weak human progesterone receptor antagonist and inhibited 5-HT transporter and $GABA_A$ receptors with IC_{50} at the micromolar level. No adverse changes were noted for safety endpoints regarding the respiratory and central nervous systems in rat following single oral administration of darolutamide up to the highest dose examined. Some cardiovascular changes (vasodilation, decrease in arterial blood pressure, slight and brief shortening of QT/QTc intervals, and transient complete AV block) were noted in anesthetized dogs but could not be confirmed in the conscious ones. No notable changes in arterial blood pressure or ECG abnormalities were seen with darolutamide in 28-day, 13- or 39-week repeated-dose toxicity studies in dogs. The hERG potassium current was only blocked at a very high concentration that is not regarded to be of physiological relevance. The same was due for the L-type calcium channel that was blocked only at rather high concentrations. Delayed gastric emptying and intestinal transit were observed in fasted male rats in a supplemental safety

pharmacology study when darolutamide was given as a solution formulation. However, no effects were seen up to the highest dose examined when suspension formulation was used.

2.2.2 Toxicological Studies

In the repeated-dose toxicity studies, the major findings observed after treatment with darolutamide in both rats and dogs were the atrophic changes in the male genital organs observed in both species in all pivotal studies, which were considered to be a consequence of the pharmacological effect of darolutamide. Darolutamide was tested in a standard genotoxicity battery, and no evidence for a relevant genotoxic potential was found. According to the disease indication, the patient population, and findings in the general toxicity studies, it is acceptable that no carcinogenicity or reproductive and developmental toxicity studies were conducted with darolutamide. Darolutamide was negative in an in vitro phototoxicity assay.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Darolutamide consists of two diastereomers [(S,R) darolutamide and (S,S) darolutamide] which interconvert via the main circulating metabolite called keto darolutamide. *In vitro*, all three substances show similar pharmacological activity.

Following repeated oral administration of 600 mg darolutamide, peak concentrations are usually reached around 4 hours in healthy volunteers. Absolute bioavailability of darolutamide given as a tablet under fasted condition is 30%. Darolutamide systemic exposure was enhanced by 2.0-2.5-fold when administered with high-fat or low-fat meal. Darolutamide exhibit nearly dose-proportional exposure at single or multiple dose range of 100 to 700 mg. After repeated oral administrations every 12 hours, steady-state concentrations were achieved by day 2~5 and the two diastereomers, (S,R)-darolutamide and (S,S)-darolutamide, was observed to transition from a 1:1 ratio in the tablet to a 1:9 ratio in plasma of nmCRPC patients.

The apparent Vd after intravenous administration is 119 L. 92% and 99.8% darolutamide and keto-darolutamide bound to plasma proteins, respectively. Darolutamide is metabolized via oxidation by CYP3A4 and glucuronidation by UGT1A9, UGT1A1, UGT1A3 and UGT2B10. In mass balance study, 63.4% of the total administered dose recovered in urine (6.7% excreted unchanged) and 32.4% recovered in feces. Based on the popPK analysis, the effective $T_{1/2}$ of darolutamide and keto darolutamide in nmCRPC patients are 19.6 and 20.0 hours, respectively. The respective effective $T_{1/2}$ values for (S,R)-darolutamide and (S,S)-darolutamide were 9 and 22 hours, respectively.

2.3.2 Interaction Studies

The results from *in vitro* studies indicated that darolutamide is not a CYP enzymes

inhibitor but it is a CYP3A4 inducer. Darolutamide is an inhibitor of BCRP, OATP1B1, OAT3, OATP1B3, MATE2K, P-gp, MATE1 in decreasing order of relevance. Darolutamide was identified as a substrate of both P-gp and BCRP.

In clinical drug interaction studies, darolutamide C_{max} and $AUC_{(0-72)}$ values were lower by 52% and 72%, respectively when concomitantly used with a combined P-gp and strong CYP3A4 inducer (rifampin) in healthy male subjects. Darolutamide C_{max} and $AUC_{(0-72)}$ values were higher by 1.36- and 1.75-fold, respectively upon concomitantly used with combined P-gp and strong CYP3A4 inhibitor (itraconazole) in healthy male subjects. As a perpetrator, darolutamide increased rosuvastatin (a BCRP, OATP1B1, OATP1B3 and OAT3 substrate) exposure by 5-fold. This effect is mainly attributed to inhibition of BCRP, but OAT1B1 and OATP1B3 contribution cannot be ruled out (see above). Darolutamide is unlikely to clinically affect PK of CYP3A and P-gp substrates.

2.3.3 Special Populations

The Pop PK analysis showed that age, body weight or gender has no clinically relevant impact on the exposure of darolutamide. In a dedicated organ impairment trial, darolutamide exposure increased by 1.9-fold and 2.5-fold in non-cancer subjects with moderate hepatic impairment (Child-Pugh B) and severe renal impairment (eGFR 15-29 mL/min/1.73 m^2), respectively. Based on the results from the Pop PK analysis, mean $AUC_{(0-12)ss}$ of darolutamide was comparable in patients with mild hepatic impairment and those with normal hepatic function. A 1.1- and 1.3-fold higher $AUC_{(0-12)ss}$ was observed in patients with mild and moderate renal impairment compared to patients with normal renal function. The PK of darolutamide has not been studied in patients with ESRD (eGFR <15 mL/min/1.73 m^2) or severe hepatic impairment (Child-Pugh C).

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

One Phase III study ARAMIS (study no.: 17712; NCT02200614) was evaluated and supported the efficacy of NUBEQA® (Darolutamide) for the treatment of patients with high risk non-metastatic castration resistant prostate cancer (nmCRPC). To entered the study, patients were required to have a PSA doubling time <10 months and PSA≧2ng/ml. The subjects were randomized in a 2:1 ratio to receive darolutamide 600 mg BID or placebo treatment. Randomization was stratified by PSA doubling time (≤6 months or >6 months) and the use of osteoclast-targeted therapy (yes or no). All subjects maintained castrate level of testosterone by ADT or surgical castration. The primary endpoint was metastasis-free survival (MFS) assessed by blinded independent central review. A total of 437 MFS events had occurred as of the cut-off date for the primary analysis. Secondary endpoints included overall

survival (OS), time to pain progression (TTPP), time to first symptomatic skeletal event (SSE), and time to initiation of first cytotoxic chemotherapy (testing hierarchical order: 1)MFS, 2)OS, 3)TTPP, 4)time to initiation of first cytotoxic chemotherapy for prostate cancer, 5)time to first SSE).

There were 1509 patients enrolled in study ARAMIS, most subjects had Gleason score≧ 7. The median PSA doubling time was 4.389 months and 4.650 months in darolutamide group and placebo group, respectively.

The study demonstrated a significant treatment effect with respect to metastasis-free survival (MFS) in the darolutamide 600 mg twice daily arm compared with the placebo arm (median MFS with baseline metastasis non-censored: 40.37 months vs. 18.43months; HR (95% CI): 0.413 (0.341; 0.500); two-sided p-value by stratified log-rank test < 0.000001). Significant and clinically meaningful benefit from darolutamide has been demonstrated. The sensitivity analyses also support the primary analysis. The efficacy result was consistent for different subgroup, including baseline PSA doubling time >6months or ≦6 months. This finding supports the potential benefit for patients with longer PSA doubling time.

At the time for the primary MFS analysis, the HR for OS interim analysis was 0.706 (95% CI 0.501, 0.994), p=0.045210. It did not meet the pre-specified significant level for the interim analysis of OS (0.0005). However, this result still favored darolutamide over placebo. Other secondary endpoints also showed the benefit of darolutamide for TTPP, time to initiation of first cytotoxic chemotherapy for prostate cancer, and time to first SSE.

2.4.2 Safety Results

Safety results of pivotal study 17712 in nmCRPC showed that darolutamide was well tolerated with a comparable incidence of TEAEs (treatment emergent adverse events) between darolutamide treated subjects and placebo treated subjects. The incidence of TEAE leading to dose modification was 14.2% in the darolutamide treatment arm. The incidence of permanent discontinuation of study treatment was comparable in both darolutamide (8.9%) and placebo (8.7%) treatment arms. . The study enrolled 12 subjects with a seizure history in darolutamide arm, and none of them had seizure during the study. Another 2 patients (0.21%) in the darolutamide arm and 1 patient (0.18%) in the placebo arm had seizure TEAE, but all events were not related to study treatments. Other TEAEs related to AR inhibitor occurred in similar incidence between darolutamide treatment and placebo treatment, except slightly higher incidence for rash and cardiac arrhythmias in darolutamide-treated subjects than placebo-treated subjects.

2.5 Bridging Study Evaluation

After repeated BID administration of 600 mg darolutamide, the PK parameters ($AUC_{0\text{-}tlast}$ or AUC) of darolutamide observed in 9 Japanese patients with prostate cancer in Study 17719 were in the same range as those in Caucasian patients with mCRPC evaluated in previous studies, but at the upper end. From population PK analysis, the descriptive comparisons of PK characteristics between Asian (Japan + Korea, N=74) and non-Asian (N=314) patients showed a 1.3-fold higher exposure among Asian patients. Based on the exposure-response analysis performed in Study 19792, the exposure difference between Asian and non-Asian patients is not considered to be clinically relevant. Overall, the PK characteristics of darolutamide are regarded as unlikely to be affected by ethnic factors.

There were 186 East Asian subjects from the global pivotal trial Study 17712 ARAMIS (account for 12% overall population). The HRs of MFS were comparable between patients from the Asia-Pacific region and the patients from non-Asia regions (0.350 and 0.423, respectively), showing a MFS benefit in East-Asian. The safety profile in patients from the Asia-Pacific region and the patients from the non-Asia regions was consistent with the safety profile observed in the overall study population.

In summary, the ethnic difference in this application is not significant. Bridging study has been waived.

2.6 Conclusion

Favorable benefit-risk profile of darolutamide was demonstrated for treatment of nmCRPC patients. To approve this NDA is suggested.

3. Post-Marketing Requirements

Provide the final analysis of study ARAMIS.