Taiwan Food and Drug Administration

Assessment Report

Trade Name：博癌癒 50 毫克膠囊(Braftovi 50mg hard capsules)/
博癌癒 75 毫克膠囊(Braftovi 75mg hard capsules)

Active Ingredient：Encorafenib

License Number： MOHW-PI 028351/ MOHW-PI 028352

Applicant：友華生技醫藥股份有限公司

Approval Date：111.10.07

Indication：

- 與 binimetinib 併用，治療帶有 BRAF V600 突變且無法切除或有轉移現象的黑色素瘤成人病人。
- 與 cetuximab 併用，治療帶有 BRAF V600E 突變且曾接受全身性療法的轉移性結腸直腸癌（CRC）成人病人。

- in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
- in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.

Background Information

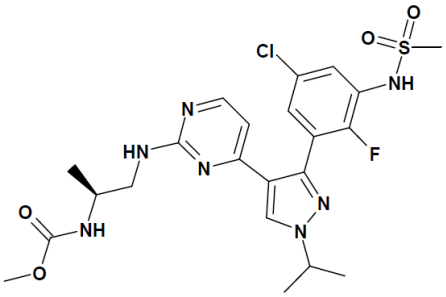
Trade Name	博癌癒 50 毫克膠囊(Braftovi 50 mg hard capsules)/ 博癌癒 75 毫克膠囊(Braftovi 75 mg hard capsules)
Active Ingredient(s)	Encorafenib
Applicant	友華生技醫藥股份有限公司
Dosage Form & Strengths	膠囊劑
Indication	- 與 binimetinib 併用，治療帶有 BRAF V600 突變且無法切除或有轉移現象的黑色素瘤成人病人。 - 與 cetuximab 併用，治療帶有 BRAF V600E 突變且曾接受全身性療法的轉移性結腸直腸癌（CRC）成人病人。 - in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. - in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.
Posology	詳見仿單
Pharmacological Category **ATC Code**	L01EC03

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The chemical name of encorafenib is methyl *N*-{(2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl) amino]propan-2-yl}carbamate. Encorafenib is a white to almost white powder. The molecular formula and the relative molecular mass for encorafenib are $C_{22}H_{27}ClFN_7O_4S$ and 540.0, respectively. It has the following structure:



The chemical structure of encorafenib is elucidated by elemental analysis, mass spectrometry, infrared spectroscopy, ultraviolet spectroscopy, ^{1}H-NMR, ^{13}C-NMR and single crystal X-ray crystallography.

The specification for encorafenib includes tests for appearance, identification, related substances, residual solvents, water content, particle size and assay.

2.1.2 Drug product

The drug product is an immediate release hard gelatin capsule for oral administration containing 50 mg or 75 mg of encorafenib. The specifications for the excipients are adequate. The specification for the drug product includes tests for appearance of capsule, appearance of capsule contents, identification, assay, degradation products, crystalline drug content, uniformity of dosage units by content uniformity, dissolution, water content and microbiological examination. Analytical methods are described and well validated.

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

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Encorafenib is a drug for the treatment of unresectable or metastatic melanoma (in combination with binimetinib) and metastatic colorectal cancer (in combination with cetuximab). Encorafenib is a selective inhibitor against BRAF^{V600E} kinase. The *in vitro* and *in vivo* pharmacology studies indicated that encorafenib blocks BRAF^{V600E} kinase and inhibits the growth of tumors with *BRAF*^{V600E} mutation but does not inhibit *BRAF*^{wt} tumor in mouse xenograft models. The xenograft studies also provided the proof of concept of the combination of encorafenib/binimetinib and encorafenib/cetuximab. Safety pharmacology studies showed a drug-related but dose-independent heart rate increase.

2.2.2 Toxicological Studies

General toxicity studies showed that encorafenib is better tolerated in monkeys than rats. When receiving the same dosage of encorafenib, the rats presented more clinical responses in skin and other organs, but the monkey did not. The NOAEL values were 20 mg/kg in rats

and monkeys. Encorafenib has no mutagenic effects but has the potential for reproductive toxicity. Decreased fetal weight and delayed skeletal development were observed in the high dose groups of the studies in both rats and rabbits. The NOAEL values were 20 mg/kg (dam) and 5 mg/kg (offspring) in rats, and 25 mg/kg (dam and offspring) in rabbits. The other studies showed that encorafenib has phototoxic potential but no skin irritation. The clinical dose is supported by clinical trials.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Encorafenib is a RAF kinase inhibitor that targets BRAF V600E, as well as wild-type BRAF and CRAF in in vitro cell-free assays, and which can combine with binimetinib to treat patients with unresectable or metastatic melanoma, or combine with cetuximab to treat patients with metastatic colorectal cancer (mCRC). The oral absorption of encorafenib was estimated about 86%. T_{max} was reached at 2 hours post-dose, and binimetinib or cetuximab did not affect this time. Besides, binimetinib or cetuximab also did not have significant impact on the AUC and C_{max} of encorafenib, indicating there was no DDI between them. The inter-subject variability was moderate to high. High-fat meal decreased the C_{max} by 36%, delayed the T_{max} by 2 hours, but have no effect on AUC; thus, Braftovi can be taken with or without food. The AUC_{inf} and C_{max} of encorafenib were approximately dose-linear over the dose range of 50 to 700 mg following a single dose administration and over the dose range of 50 to 550 mg at steady-state. After repeat oral use, the exposure of encorafenib decreased about by half, this may be due to the auto-induction of CYP3A4. When administered encorafenib 450 mg QD combined with binimetinib 45 mg BID, the apparent volume of distribution was 164 L, terminal half-life ($T_{1/2}$) was 3.52 hours, and clearance was 13.9 L/h on day 1, 32.3 L/h (58.9%) at steady-state. The protein binding of encorafenib was 86% in vitro. The blood-to-plasma concentration ratio was 0.58. CYP3A4 was the main metabolism enzyme (83.3%), CYP2C19 (~16%) and CYP2D6 (0.71%) also played a minor role in elimination of encorafenib. An equal mean of 47.25% of the radioactivity dose was recovered in urine and in feces. Unchanged encorafenib were accounted for 1.8% and 5.0% of dose in excreta, respectively, indicating metabolism was primarily elimination pathway for encorafenib.

2.3.2 Interaction Studies

Encorafenib is substrate of P-gp and CYP3A4. The DDI study showed that posaconazole (a strong CYP3A4 inhibitor) or diltiazem (a moderate CYP3A4 inhibitor) increased AUC of encorafenib; thus, it is advised to avoid combination with a strong or moderate CYP3A4 inhibitor. Although the effect of a CYP3A4 inducer on encorafenib exposure has not been studied, it was predicted that the exposure of encorafenib will be decreased. Thus, avoid coadministration of encorafenib with strong or moderate CYP3A4 inducers. No dose adjustment was required when co-administered with rabeprazole (PPI).

2.3.3 Special Populations

No dose adjustment was required based on gender, age, body weight and mild to moderate (CLcr 30 to < 90 mL/min) renal impairment. However, for severe (CLcr <30 mL/min) renal impairment subjects, no recommended dosing regimen can be made due to lack of data. In mild hepatic (Child-Pugh Class A) impairment subjects, the AUC and $AUC_{inf,unbound}$ increased by 25% and 55%, respectively. Considering encorafenib was extensively metabolized in liver, it is advised to reduce dose to 300 mg QD in these patients. A recommended dosage has not been established in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, the Sponsor provided one well-controlled study (mek162b2301) to support the efficacy of encorafenib for the indication of treating melanomas and provided one well-controlled study (ARRAY-818-302) to support the efficacy of encorafenib for the indication of treating Colorectal cancer.

Study mek162b2301 was a multicenter, randomized, open-label, Phase 3 study. The study met its primary endpoint as the combination of encorafenib 450 mg QD and binimetinib 45 mg BID significantly improved PFS by more than doubling the median PFS vs. vemurafenib alone (HR=0.54, 95% CI: 0.41, 0.71; 1-sided p < 0.001). The key secondary endpoint (PFS of encorafenib 450 mg QD and binimetinib 45 mg BID vs. encorafenib) missed achieving formal statistical significance (HR=0.75, 95% CI: 0.56, 1.00; 1-sided p=0.026).

As the results of the key secondary analysis (PFS, Combo 450 vs. encorafenib) were not statistically significant, this OS analysis is considered descriptive in nature. An interim OS analysis (cut-off date 07 November 2017), demonstrated a statistically significant improvement in OS for Combo 450 compared with vemurafenib (HR= 0.61, 95% CI: 0.47, 0.79, 1-sided p < 0.001).

Study ARRAY-818-302 is an ongoing (enrollment complete) multicenter, randomized, open-label, 3-arm, Phase 3 study. The primary efficacy endpoints were OS and ORR by RECIST version 1.1 The secondary endpoint was PFS. Results showed that BRAF V600E-mutant patients with mCRC in the Doublet arm (ENCO + CETUX) demonstrated statistically significant improvements in OS [Cut-off date(11Feb2019): HR=0.60, 95% CI: 0.45, 0.79, 1-sided p =0.0002; Cut-off date(15Aug2019): HR=0.61, 95% CI: 0.48, 0.77, 1-sided p <0.0001; Cut-off date(05May2020): HR=0.63, 95% CI: 0.51, 0.78, 1-sided p <0.0001], ORR by BICR (OR=13.72,

95% CI: 3.15, 59.80, 1-sided p <0.0001) and PFS (HR=0.40, 95% CI: 0.31, 0.52, 1-sided p <0.0001) over the Control arm.

2.4.2 Safety Results

Melanoma with BRAF mutation

Please refer to the review report of binimetinib.

mCRC with BRAF mutation

The overall AE profile of the Doublet arm was better than the Triplet and Control arms in Study ARRAY-818-302. A lower percentage of Grade ≥3 AEs in the Doublet vs the Triplet (57.4% vs 65.8%) A lower incidence of SAEs for the Doublet vs the Triplet (39.8%vs 49.5%) and a similar incidence of on-treatment deaths with most on-treatment deaths being due to disease progression in both arms.

The most frequently reported AEs (> 25% patients) were mostly similar across the 3 treatment arms. The most common AEs were diarrhea, nausea, fatigue, decreased appetite, dermatitis acneiform, abdominal pain, vomiting, asthenia and arthralgia. More MEK inhibitor related toxicities (retinopathy, LVEF decrease and CK elevation were observed in the Triplet arm compared with the Doublet arm. The majority of these events were Grade 1 and 2 in severity and were generally manageable in both treatment arms.

In the Doublet arm, the most frequently reported SAEs (> 2%) were intestinal obstruction, diarrhea, pulmonary embolism, acute kidney injury and nausea, vomiting, abdominal pain, anemia and ileus. Most on study deaths were due to disease progression.

In the Doublet arm, decreased hemoglobin was the most common new or worsened hematology abnormality (39.4% with 5.6% of Grade ≥3); followed by decrease in lymphocyte count (25.5%) and increase in aPTT (13.0%) but were mostly Grade 1 or 2. Clinically notable shifts in >10.0% of patients occurred for the serum chemistry parameters of increased glucose (13.5%) in the Doublet arm. New QTcF > 500 ms was reported for 2.8% of patients at risk in the Doublet arm, which was higher than in other two arms. However, most of the abnormal findings were isolated events, found at a single study visit.

In conclusion, combination of encorafenib and cetuximab is well tolerated with manageable toxicities, consistent with the known safety of each component.

2.5 Bridging Study Evaluation

No dedicated ethnic PK study was conducted in Asian country to be used to a head-to-head comparison with that from Non-Asian country. However, the PK data from Asian subjects in

several individual study showed that there was no significant PK difference between East Asian subject and non-East Asian subject. Also, the posology of encorafenib and binimetinib in PMDA labeling was same as that in foreign country. Overall, the ethnic difference was negligible from PK point of view.

Melanoma with BRAF mutation

Please refer to the review report of binimetinib.

mCRC with BRAF mutation

The sponsor provided East-Asian subgroup analysis in Study ARRAY-818-302 to support BSE for this proposed indication.

A total of 84 Asian patients were enrolled in Study ARRAY-818-302. Of them, 23 patients from East-Asian region were treated by Doublet therapy. These 23 East Asian patients were younge and had better PS, lower tumor marker at baseline than patients from the rest of world. The efficacy results in East Asians showed the tumor response and overall survival time were similar to the results in other ethnics. The safety interpretation was restricted due to the limited number of East Asian patients treated with Doublet therapy. In overall, safety profile in East Asian patients showed less AE ≥ grade 3 and SAEs compared to other ethnics. The AEs and SAEs related to cytopenia were higher in East Asians. However, cytopenia is a manageable risk at clinical practice.

Ethnic difference with clinically relevant impact was not observed. Bridging study was waived.

2.6 Conclusion

Based on review of the submitted package, the review team considered encorafenib demonstrates a favorable risk-benefit profile with enough evidence to recommend regular approval for the following indication:

Encorafenib is indicated:

- in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
- in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.

3. Post-Marketing Requirements

1) Submit final report of W00090GE101 and ARRAY-818-103 after study completion. Amend the label content according to the results.
2) Submit final report of ARRAY-162-115 after study completion.