Cost-effectiveness of encorafenib (Braftovi®), in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of encorafenib (Braftovi®). Following assessment of the Applicant's submission, the NCPE recommends that encorafenib (Braftovi®) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. The HSE asked the NCPE to carry out an evaluation of the Applicant's (Pierre Fabre) Health Technology Assessment dossier on encorafenib (Braftovi®). The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **January 2022**

Summary

In June 2021, Pierre Fabre submitted a dossier investigating the clinical effectiveness, cost effectiveness and potential budget impact of encorafenib (Braftovi®), in combination with cetuximab (encorafenib + cetuximab), for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy. Reimbursement is sought on the High Tech Drug Arrangement.

It is estimated that between 8% and 12% of the population with metastatic colorectal cancer have a BRAF mutation, of which the majority are V600E mutations. The presence of a BRAF V600E mutation must be confirmed prior to the initiation of encorafenib + cetuximab.

Encorafenib is a protein kinase inhibitor which specifically targets the BRAF protein and is an antineoplastic agent. It is the first BRAF-targeted therapy to be licensed for this indication. It is administered in combination with intravenous cetuximab. Treatment is continued until disease progression or until development of unacceptable toxicity.

The Applicant anticipates that encorafenib + cetuximab will be used, in accordance with its licence, in the second line (or later) treatment setting. Clinical opinion obtained by the Applicant indicates that the most relevant comparator in Ireland is FOLFIRI (oxaliplatin, irinotecan and fluorouracil), either alone or in combination with cetuximab (FOLFIRI + cetuximab) or bevacizumab (FOLFIRI + bevacizumab). The Applicant considers FOLFIRI + cetuximab to be the most relevant comparator (Applicant base case analysis). The Review Group considers FOLFIRI to be the most relevant comparator based on clinical guidelines and clinical opinion obtained by the Applicant.

1. Comparative effectiveness of encorafenib

The pivotal trial supporting product registration is the on-going, open-label, phase three randomised controlled trial, BEACON CRC. Eligible participants were adults, with metastatic colorectal cancer and confirmed BRAF V600E mutation, who had progressed following one or two treatment regimens. Patients were randomised to one of three treatment arms

(1:1:1): encorafenib in combination with binimetinib and cetuximab (n=224; triplet therapy); encorafenib + cetuximab (n=220; doublet therapy) and; FOLFIRI + cetuximab or irinotecan + cetuximab (n=221; control arm). Encorafenib was administered orally at 300mg once daily. Cetuximab was administered intravenously at 400mg/m^2 on day one with subsequent infusions administered at 250mg/m^2 once weekly, in accordance with the licensed dosing regimen. The co-primary endpoints of the trial are overall survival (OS) and overall response rate (ORR) in the triple therapy arm compared with the control arm. A key secondary endpoint is OS in the doublet arm versus the control arm, which is of most relevance to this submission. Progression-free survival (PFS) in the doublet arm compared with the control arm is a secondary endpoint. Health-related quality of life (HRQoL) data, including the EQ-5D-5L, were collected. The Applicant withdrew the application for regulatory approval for the triplet combination. The efficacy and safety in the doublet arm (encorafenib + cetuximab) versus the control arm (FOLFIRI + cetuximab or irinotecan + cetuximab) are of relevance for this submission. Clinicians, consulted by the Applicant, indicated that the licensed dose for cetuximab (that is used in BEACON CRC) is not always used in clinical practice in Ireland. A dose of 500mg/m^2 once every two weeks is also used; this dose is unlicensed. NCCP Chemotherapy Regimens describe both dose regimens.

In the second interim analysis, with a data cut-off date of August 2019, doublet therapy was associated with an OS benefit compared with the control arm (hazard ratio (HR) 0.61 (95% confidence interval (CI) 0.48 to 0.77; one-sided p-value < 0.0001)). A PFS benefit for the doublet arm versus the control arm was demonstrated (HR 0.44 (95% CI 0.35 to 0.55; one-sided p-value < 0.0001)). Efficacy parameters, in the cost-effectiveness model, were informed by a more recent data cut (May 2020). The Applicant identified these data as academic in confidence.

The Review Group had concerns relating to the direct comparative evidence from the BEACON CRC trial. Most notably there is a lack of direct comparative evidence with the most relevant comparator, FOLFIRI. The open-label design of the study is also a concern.

The Applicant performed an indirect treatment comparison (ITC). Results suggested that encorafenib + cetuximab is associated with a survival benefit in comparison with FOLFIRI (OS

HR 2.50 (95% CI 1.19 to 5.26) and PFS HR 3.13 (95% CI 1.41 to 7.14)). Due to a paucity of data, the Applicant assumed equivalent efficacy between FOLFIRI + bevacizumab and the control arm of the BEACON CRC trial. The Review Group had concerns regarding the validity of equivalent efficacy assumptions and the quality of the data used in the ITC.

2. Safety of encorafenib

The safety analysis of encorafenib + cetuximab was conducted in 216 patients from the BEACON CRC trial. Based on the August 2019 data cut, the mean duration of exposure to the doublet regimen was 25.17 weeks (standard deviation 18.19 weeks); the trial is ongoing. Mean relative dosing intensities of encorafenib and cetuximab were 87.6% and 86.9% respectively. The most frequent AEs in the control arm were diarrhoea (48.7%), nausea (43.5%), dermatitis acneiform (39.9%) and vomiting. The most frequent AEs in the doublet arm were diarrhoea (38.4%), nausea (38%), fatigue (33.3%), decreased appetite (31%) and dermatitis acneiform (39.9%). Grade ≥3 treatment-related adverse events (AEs) were reported in 42% and 21.3% of patients in the control and doublet arms respectively. Grade ≥ 3 AEs, reported in at least 5% of patients in the control arm, were: diarrhoea (10.4%), neutropenia (10.4%), neutrophil count decreased (8.3%), anaemia (6.7%), abdominal pain (5.2%) and asthenia (5.2%). The grade ≥ 3 AE, reported in at least 5% of patients in the doublet arm, was anaemia (5.6%). The most frequently reported serious AEs in the control arm were diarrhoea (5.2%), intestinal obstruction (3.6%) and abdominal pain (2.1%). The most frequently reported serious AEs in the doublet arm were intestinal obstruction (5.1%), abdominal pain, urinary tract infection and cancer pain (2.3% each). AEs that required a dose reduction were experienced by 31.6% and 12% of patients in the control and doublet arms respectively. AEs that led to discontinuation of any study treatment were experienced by 17.1% and 12% of patients in the control and doublet arms respectively.

3. Cost effectiveness of encorafenib

The population in the cost-effectiveness analysis were adult patients with metastatic colorectal cancer and BRAF V600E mutation who have received prior systemic therapy. This is aligned with the licensed indication and the population in the BEACON CRC trial. A partitioned survival model was utilised, consisting of three mutually exclusive health states: progression-free, progressed disease and death. Cycle length was one calendar month; half-

cycle correction was applied. Direct evidence for encorafenib + cetuximab versus FOLFIRI + cetuximab was derived from the doublet and control arms of BEACON CRC respectively. The Review Group note that the trial control arm comprised patients on FOLFIRI + cetuximab or irinotecan + cetuximab. Parametric extrapolations from the BEACON CRC trial OS and PFS data were used to estimate the proportion of the population in the three health states. The FOLFIRI + bevacizumab arm was assumed to have equivalent efficacy to the control arm of the BEACON CRC trial. The HRs generated from the ITC were applied to the extrapolated curves for the comparison with FOLFIRI. Treatment durations for encorafenib + cetuximab and FOLFIRI + cetuximab were estimated from extrapolated time-to-treatment discontinuation (TTD) data from BEACON CRC. TTD for FOLFIRI + bevacizumab was assumed to be equivalent to that of FOLFIRI + cetuximab. For FOLFIRI, TTD was assumed to be equivalent to PFS. Health-state utilities were generated from EQ-5D-5L data, from BEACON CRC, mapped to EQ-5D-3L. Costs included drug acquisition costs (assuming a Framework Agreement rebate of 5.5%), intravenous chemotherapy administration costs, healthcare resource use costs, subsequent treatment costs and AE costs. The cost of cetuximab, in the model, was reflective of the unlicensed dosing regimen of 500mg/m^2 once every two weeks (as described in the NCCP Chemotherapy Regimens). The Review Group had concerns regarding certain modelling assumptions, including the use of a piecewise model and proportional hazards for comparators in the ITC. The method for deriving mean health state utility values was considered unreliable. Results from several scenario analyses were provided.

The Review Group consider FOLFIRI to be the most relevant comparator; the Applicant had considered this to be FOLFIRI + cetuximab. The Review Group corrected input errors in the Applicant analysis. The Review Group implemented a number of alternative assumptions in the NCPE adjusted base case analysis including; assuming a RDI of 100%; accounting for wastage of encorafenib; including vial wastage and; updated costs for intravenous drug administration and outpatient attendance. The Review Group also applied costs associated with testing for the presence of a BRAF V600E mutation for the comparisons with FOLFIRI and FOLFIRI + bevacizumab. These testing costs are currently incurred in Ireland when considering treatment with FOLFIRI + cetuximab. Thus, it is unnecessary to include this cost in the comparison with FOLFIRI + cetuximab.

Deterministic results based on the NCPE adjusted cost-effectiveness analyses are presented in Table 1.

Table 1 Deterministic results of the NCPE adjusted analyses

Treatment strategy	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)
*Encorafenib + cetuximab	97,592 *93,592	1.022			
^FOLFIRI	20,769	0.421	78,335	0.601	130,246/QALY
FOLFIRI + bevacizumab	30,048	0.616	67,544	0.406	166,314/QALY
FOLFIRI + cetuximab	34,343	0.616	59,249	0.406	145,890/QALY

QALY: quality adjusted life year; **ICER**: incremental cost effectiveness ratio
*Patients in both arms of the comparison with FOLFIRI + cetuximab incur the cost of testing for the BRAF V600E mutation; testing costs cancel out across arms. The total cost of 'encorafenib + cetuximab' input in the model in the comparison with FOLFIRI + cetuximab is lower (€93,592) than the input cost of this regimen (€97,592) in the other comparisons.
^Base case comparator in the NCPE adjusted analyses
Total costs and QALYs presented are discounted (4%). Drug costs are estimated based on the Framework Agreement rebate of 5.5%.
Figures in the table are rounded, and so calculations may not be directly replicable.

Deterministic results based on the Applicant corrected cost-effectiveness analyses are presented in Table 2.

Table 2 Deterministic results of the Applicant corrected cost-effectiveness analyses

Treatment strategy	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)
Encorafenib + cetuximab	86,211	1.022			
FOLFIRI	20,769	0.421	65,441	0.601	108,809/QALY
FOLFIRI + bevacizumab	28,476	0.616	57,735	0.406	142,161/QALY
^FOLFIRI + cetuximab	32,122	0.616	54,089	0.406	133,184/QALY

QALY: quality adjusted life year; **ICER:** incremental cost-effectiveness ratio;
^Base case comparator in the Applicant corrected analysis
Total costs and QALYs presented are discounted (4%). Drug costs are estimated based on the Framework Agreement rebate of 5.5%.
Figures in the table are rounded, and so calculations may not be directly replicable.

Sensitivity analyses on the NCPE-adjusted analysis. Probabilistic mean ICERs are similar to deterministic ICERs. When the cost of encorafenib is set to zero, all incremental cost-effectiveness ratios (ICERs), remain above the willingness to pay threshold of €45,000/QALY. When all four treatment strategies are concurrently compared, the probability of encorafenib + cetuximab being the most cost-effective treatment strategy is 0% at

thresholds of €20,000/QALY and €45,000/QALY. As mentioned previously, the comparison with FOLFIRI + cetuximab was informed by the control arm of BEACON CRC. In a sensitivity analysis, data from the subgroup in the control arm who had received FOLFIRI + cetuximab was instead used. The model was robust to this change.

4. Budget impact of encorafenib

The price to wholesaler per pack of 42 capsules of encorafenib 75mg is €1,403.28. The Applicant estimated the per-patient treatment cost of encorafenib + cetuximab to be €73,409 including VAT (using the estimated TTD of 9.53 months from the cost-effectiveness model). The Review Group estimated the per-patient treatment cost to be €86,589, including VAT, assuming wastage. The Applicant anticipates that 24 patients will receive treatment with encorafenib + cetuximab in year one, increasing to 44 in year five. The Review Group considered this to an underestimate and assumed 30 patients in year one, increasing to 55 in year five. The Applicant estimates the five-year cumulative gross budget impact of encorafenib + cetuximab to be €13.81 million, including VAT. The Review Group estimates the five-year gross impact to be €20.42 million, including VAT. The Applicant estimates the five-year net drug budget impact to be €12.38 million, including VAT. The Review Group estimates the five-year net impact to be €17.69 million, including VAT.

5. Patient organisation submissions

No patient submissions were received.

6. Conclusion

The NCPE recommends that encorafenib, in combination with cetuximab, not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.