

5.05 ENCORAFENIB, Capsules, 50mg and 75mg, Braftovi®; and BINIMETINIB, Tablets, 15mg, Mektovi®, Pierre Fabre Australia.

1 Purpose of Application

- 1.1 The submission requested an Authority Required (STREAMLINED) listing for encorafenib in combination with binimetinib for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation. This is the first application to PBAC for encorafenib and binimetinib in combination. Listing is not sought for either component as monotherapy.
- 1.2 The requested listing was based on a cost-minimisation analysis of encorafenib+binimetinib to dabrafenib+trametinib and to vemurafenib+cobimetinib. The key components of the clinical issue addressed by the submission are summarised below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
Intervention	Treatment (oral) in combination as follows: Encorafenib 450 mg (six 75 mg capsules) once daily Binimetinib 45 mg (three 15 mg tablets) twice daily approximately 12 hours apart
Comparator	The submission nominated other PBS-listed BRAF inhibitor/MEK inhibitor combinations as the comparator. A primary comparison with dabrafenib+trametinib supported by a secondary comparison with vemurafenib+cobimetinib was presented in the submission.
Outcomes	Primary: PFS Secondary: OS; ORR; best overall response, time to response, duration of response, patient-reported outcomes (FACT-M, EORTC QLQ-C30, EQ-5D); incidence of adverse events
Clinical claim	Encorafenib+binimetinib is at least non-inferior to dabrafenib+trametinib in terms of effectiveness and safety. Encorafenib+binimetinib is at least non-inferior to vemurafenib+cobimetinib in terms of effectiveness and safety.

ORR = overall response rate; OS = overall survival; PFS = progression free survival

Source: Table 1.1, p16 of the submission

For more details on the PBAC's view, see Section 7 PBAC outcome.

2 Requested listing

- 2.1 The requested PBS listings are shown below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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Requested restriction – encorafenib 50 mg; encorafenib 75 mg (initial and continuing)

Name, restriction, manner of administration, form	Maximum quantity (packs)	No. of repeats	DPMQ	Proprietary name and manufacturer
Initial treatment:				
ENCORAFENIB 50 mg capsule, 28	9	3	\$ [TBD]	BRAFTOVI®, Pierre Fabre
ENCORAFENIB 75 mg capsule, 42	4	3	\$ [TBD]	
Continuing treatment:				
ENCORAFENIB 50 mg capsule, 28	9	5	\$ [TBD]	BRAFTOVI®, Pierre Fabre
ENCORAFENIB 75 mg capsule, 42	4	5	\$ [TBD]	

\$(TBD) = price to be decided, price related to proposed special price arrangement

Category / Program	General Schedule
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial <i>treatment</i>
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be positive for a BRAF V600 mutation, AND Patient must be receiving PBS-subsidised binimetinib concomitantly for this condition; AND The condition must not have been treated previously with PBS subsidised therapy; OR Patient must have developed intolerance to another BRAF inhibitor of a severity necessitating permanent treatment withdrawal, AND Patient must have a WHO performance status of 2 or less.
Administrative Advice:	A patient who has had progressive disease when treated with another BRAF inhibitor is not eligible to receive PBS-subsidised treatment with this drug. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

Treatment phase:	Continuing <i>treatment</i>
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug, AND Patient must be receiving PBS-subsidised binimetinib concomitantly for this condition; AND Patient must have stable or responding disease
Administrative Advice:	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug <i>A patient who has had progressive disease when treated with another BRAF inhibitor is not eligible to receive PBS-subsidised treatment with this drug.</i> No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

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Requested restriction – binimetinib 15 mg (initial and continuing)

Name, restriction, manner of administration, form	Maximum quantity (packs)	No. of repeats	DPMQ	Proprietary name and manufacturer
Initial treatment: BINIMETINIB 15 mg tablet, 84	2	3	\$ [TBD]	MEKTOVI®, Pierre Fabre
Continuing treatment: BINIMETINIB 15 mg tablet, 84	2	5	\$ [TBD]	MEKTOVI®, Pierre Fabre

\$(TBD) = price to be decided, price related to proposed special price arrangement

Category / Program	General Schedule
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial <i>treatment</i>
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must be receiving PBS-subsidised encorafenib concomitantly for this condition; AND Patient must not have had progressive disease when treated with a BRAF inhibitor.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

Treatment phase:	Continuing <i>treatment</i>
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug, AND Patient must be receiving PBS-subsidised encorafenib concomitantly for this condition, AND Patient must have stable or responding disease
Administrative Advice:	A patient who has had progressive disease when treated with this drug is no longer eligible for PBS subsidised treatment with this drug. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

- 2.2 It was noted in the submission that a Special Pricing Arrangement (SPA) and a Risk Sharing Arrangement (RSA) are currently in place for the comparators (dabrafenib+trametinib and vemurafenib+cobimetinib). The submission's cost-minimisation analysis was based on the published price of these targeted combination therapies. The submission stated that the effective price will be made available post a positive PBAC recommendation.
- 2.3 The proposed listing was for patients with WHO 0-2 status, which was consistent with the comparator restrictions. However, the clinical evidence for the proposed combination only included patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. The PBAC considered a WHO 0-2 status was appropriate for inclusion in the initiation restriction.

- 2.4 The proposed listing allowed patients with non-cutaneous melanoma (that is, melanoma of non-skin sites such as mucosa) to be treated. The key trial COLUMBUS recruited patients with cutaneous melanoma or melanoma of unknown origin.

For more details on the PBAC's view, see Section 7 PBAC outcome.

3 Background

Registration status

- 3.1 TGA status at time of PBAC consideration: Encorafenib+binimetinib remains under evaluation by the TGA.
- 3.2 The submission was made under TGA/PBAC Parallel Process. The TGA delegate's overview was available at the time of PBAC for consideration. The overview indicated that consideration at the ACPM meeting in October 2018 was not required to register encorafenib+binimetinib.
- 3.3 The indication sought for both encorafenib and binimetinib is:
"Encorafenib in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation."

Previous PBAC consideration

- 3.4 There have been no previous submissions for either encorafenib or binimetinib.
- 3.5 Dabrafenib was recommended for listing on the PBS in July 2013. The combination of dabrafenib+trametinib was recommended in November 2014. The combination of vemurafenib+cobimetinib was considered to be non-inferior to dabrafenib+trametinib by the PBAC in March 2016.

4 Population and disease

- 4.1 Melanoma is the third most common cancer in Australia. Advanced melanoma has a median survival of around six to nine months*. In 2015, there were 1,520 deaths attributed to melanoma of the skin†. The most common mutation identified for metastatic melanoma is BRAF V600, occurring in between 40 to 60 percent of cases‡.
- 4.2 BRAF/MEK inhibitors are currently the standard first-line treatment for unresectable Stage III or Stage IV malignant melanoma patients who have positive BRAF V600

* Ipilimumab public summary document, November 2012 PBAC meeting

† AIHW. Australian Cancer Incidence and Mortality (ACIM) books: melanoma of the skin. 2017. Canberra: Australian Institute of Health and Welfare

‡ Hannan EJ, O'Leary DP, MacNally SP, et al. The significance of BRAF V600E mutation status discordance between primary cutaneous melanoma and brain metastases: The implications for BRAF inhibitor therapy. *Medicine (Baltimore)* 2017;96(48):e8404

mutations. The currently PBS-listed BRAF/MEK inhibitors are dabrafenib+trametinib and vemurafenib+cobimetinib. The submission requested encorafenib+binimetinib as an alternative to existing listed treatments. The proposed listing is the same as for the other two combinations, and would offer a third option for first line treatment of patients with unresectable Stage III or Stage IV (metastatic) BRAF V600 mutation positive melanoma.

- 4.3 The submission did not propose monotherapy for the BRAF inhibitor (encorafenib). In comparison, the current PBS listings permit monotherapy with the BRAF inhibitors vemurafenib and dabrafenib. The current place in therapy for BRAF inhibitors has moved away from monotherapy in favour of use in combination with a MEK inhibitor according to current Australian melanoma guidelines⁵.

For more details on the PBAC's view, see Section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated PBS-listed combinations of BRAF/MEK inhibitors as the comparators:

- dabrafenib+trametinib was nominated as the primary comparator; and
- vemurafenib+cobimetinib was nominated as a secondary comparator.

- 5.2 The ESC considered that the nominated comparators were appropriate.

For more details on the PBAC's view, see Section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (6), health care professionals (6) and organisations (3) via the Consumer Comments facility on the PBS website. The consumer comments described a range of benefits of treatment with encorafenib+binimetinib including fewer side effects and prolonged survival.

- 6.3 The PBAC noted the advice received from the Melanoma Institute, Australia supporting the access of encorafenib+binimetinib for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation in clinical practice. The PBAC

⁵ Cancer Council Australia Melanoma Guidelines Working Party. Clinical practice guidelines for the diagnosis and management of melanoma. Sydney: Cancer Council Australia 2018. Available from: <https://wiki.cancer.org.au/australia/Guidelines> (accessed August 2018)

noted that this advice was supportive of the evidence provided in the submission.

- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the encorafenib+binimetinib submission, on the basis of phase III clinical evidence. The PBAC noted that the MOGA considered that encorafenib+binimetinib appeared less toxic than the comparators based on evidence presented in the COLUMBUS trial.
- 6.5 The MOGA Melanoma Expert Group expressed further support for the encorafenib+binimetinib submission, stating it was the preferred BRAF/MEK combination for melanoma due to improved efficacy and reduced toxicity.

Clinical trials

- 6.6 The submission was based on indirect comparisons of encorafenib+binimetinib versus dabrafenib+trametinib or vemurafenib+cobimetinib via a BRAF inhibitor (vemurafenib or dabrafenib) as the common reference. The following trials were presented:
- COLUMBUS trial: a Phase III, randomised, open-label, multicentre trial in patients with unresectable or metastatic (Stage IIIB, IIIC or IV) BRAF V600-mutant melanoma comparing encorafenib+binimetinib to vemurafenib monotherapy and/or encorafenib monotherapy (n=577);
 - COMBI-V trial: a Phase III, randomised, open-label trial comparing the combination of dabrafenib and trametinib to vemurafenib in patients with unresectable or metastatic (Stage IIIC or Stage IV) BRAF V600E/K mutation positive cutaneous melanoma (n=704);
 - COMBI-D trial: a Phase III, randomised, double-blinded trial comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in patients with unresectable or metastatic (Stage IIIC or Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma (n=423);
 - coBRIM trial: a Phase III, double-blind, placebo-controlled trial of vemurafenib versus vemurafenib plus cobimetinib in BRAF V600-mutation positive patients with unresectable locally advanced or metastatic (Stage IIIC or Stage IV) melanoma (n=495).
- 6.7 The COLUMBUS trial was intended as a three-arm trial to compare:
- Combo 450: encorafenib (450 mg once daily) + binimetinib (45 mg twice daily);
 - Vemurafenib monotherapy (at the recommended dose; 960 mg twice daily); and
 - Encorafenib monotherapy at 300 mg once daily.
- 6.8 Part 2 of COLUMBUS was introduced by protocol amendment in November 2014, and explored:
- Combo 300: encorafenib (300 mg once daily) + binimetinib (45 mg twice daily); and
 - Encorafenib monotherapy at 300 mg once daily.

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- 6.9 Only Part I of the COLUMBUS trial provided data for Combo 450 and the common reference arm (vemurafenib monotherapy) which were used in the indirect comparison.
- 6.10 In COLUMBUS, 30% of patients received prior immunotherapy, largely in the adjuvant setting following resection but also including a small number treated in first line with monoclonal antibodies (approximately 5% of COLUMBUS patients). This is unlikely to be representative of the current PBS population. Adjuvant treatment was mostly with interferon in this trial, which is no longer recommended for this use in Australia.
- 6.11 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports^a presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Encorafenib+ binimetinib		
COLUMBUS (NCT01909453)	A 2-part phase III randomised, open label, multicentre study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial	Part 1 CSR, Feb 2017; addendum, Feb 2018; OS results, Feb 2018; efficacy update, Mar 2018 Part 2, May 2017 <i>Lancet Oncol</i> 2018; 19(5): 603-615
Dabrafenib+trametinib		
COMBI-V (NCT01597908)	A phase III, randomised, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. Grob JJ, Amonkar MM, Karaszewska B, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial Long GV, Grob JJ, Nathan P, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials Robert C, Karaszewska B, Schachter J, et al. Two year estimate of overall survival in COMBI-v, a randomized, open-label, phase III study comparing the combination of dabrafenib (D) and trametinib (T) with vemurafenib (Vem) as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma (conference abstract 3301) Robert C, Karaszewska B, Schachter J, et al. Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with	Protocol amendment. August 2014 <i>N Engl J Med</i> 2015; 372(1): 30-39 <i>Lancet Oncol</i> 2015; 16(13): 1389-1398 <i>Lancet Oncol</i> 2016; 17(12): 1743-1754 <i>Eur J Cancer</i> 2015; 51(Suppl. 3): S663 <i>Ann Oncol</i> 2016; 27 (Suppl. 6): vi552–vi587

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Trial ID	Protocol title/ Publication title	Publication citation
	unresectable or metastatic BRAF V600E/K-mutant cutaneous melanoma (conference abstract LBA40)	
COMBI-D (NCT01584648)	<p>A phase III, randomised, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation-positive cutaneous melanoma</p> <p>Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma</p> <p>Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial</p> <p>Schadendorf D, Amonkar MM, Stroyakovskiy D, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma</p> <p>Menzies AM, Ashworth MT, Swann S, et al. Characteristics of pyrexia in BRAFV600E/K metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial</p> <p>Long GV, Grob JJ, Nathan P, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials</p> <p>Long GV, Flaherty KT, Stroyakovskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study</p>	<p>Protocol amendment. October 2013</p> <p><i>N Engl J Med</i> 2014; 371(20): 1877-1888</p> <p><i>Lancet</i> 2015; 386(9992): 444-451</p> <p><i>Eur J Cancer</i> 2015; 51 (7): 833-840</p> <p><i>Ann Oncol</i> 2015; 26(2): 415-421</p> <p><i>Lancet Oncol</i> 2016; 17(12): 1743-1754</p> <p><i>Ann Oncol</i> 2017; 28(7): 1631-1639</p>
Vemurafenib+cobimetinib		
coBRIM (NCT01689519)	<p>Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma</p> <p>Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial</p> <p>de la Cruz-Merino L, Di Guardo L, Grob JJ, et al. Clinical features of serous retinopathy observed with cobimetinib in patients with BRAF-mutated melanoma treated in the randomized coBRIM study. <i>Journal of Translational Medicine</i></p> <p>Dréno B, Ribas A, Larkin J, et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study</p> <p>Dréno B, Ascierto PA, Atkinson V, et al. Health-related quality of life impact of cobimetinib in combination with vemurafenib in patients with advanced or metastatic BRAFV600 mutation-positive melanoma</p>	<p><i>N Engl J Med</i> 2014; 371(20): 1867-76</p> <p><i>Lancet Oncol</i> 2016; (17(9): 1248-1260</p> <p><i>J Transl Med</i> 2017; 15(1): 146</p> <p><i>Ann Oncol</i> 2017; 28(5): 1137-1144</p> <p><i>Br J Cancer</i> 2018; 118(6): 777-784</p>

^a Conference abstracts which were not used in the submission are not presented in this table.

Source: Table 2.5, p51 and Table 2.9, pp54-56 of the submission.

6.12 The indirect comparison of encorafenib+binimetinib versus the PBS-listed BRAF+MEK inhibitors relied on the results of the Part I of COLUMBUS and the published data for the COMBI-V, COMBI-D and coBRIM trials previously presented to PBAC for the

respective comparators. Since the PBAC's last consideration of these comparator medicines, further publications have appeared in the literature with updated outcomes data for the comparator trials COMBI-D, COMBI-V and CoBRIM.

6.13 The key features of the randomised trials included in the indirect comparison are summarised in the table below.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/duration	Risk of bias ^a	Patient population	Outcomes ^b
Encorafenib+binimetinib vs. vemurafenib					
COLUMBUS	577 ^c	R, MC, OL 30 months ^d	Low	Unresectable Stage IIIb, IIIc or Stage IV cutaneous melanoma or melanoma of unknown primary	PFS, OS
Dabrafenib+trametinib vs. dabrafenib					
COMBI-D	423	R, MC, DB >20 months ^e	Low	Previously untreated unresectable Stage IIIc or Stage IV cutaneous melanoma	PFS, OS
Dabrafenib+trametinib vs. vemurafenib					
COMBI-V	704	R, MC, OL 23 months ^f	Low	As above	PFS, OS
Vemurafenib+cobimetinib vs. vemurafenib					
coBRIM	495	R, MC, DB 19 months	Low	As above	PFS, OS

DB = double blind; MC = multi-centre; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised

^a Although the risk of bias within each trial was considered low, there was some potential for bias in the indirect comparison, given issues with transitivity of the trials

^b PFS assessed by blinded independent review committee (BIRC) using Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) was reported in COLUMBUS and coBRIM. Investigator-assessed PFS was reported by all four trials.

^c Part 1 of the trial

^d Median duration of follow-up for Part 1 of COLUMBUS was 30 months for the COMBO 450 arm, 16 months for the vemurafenib arm and 20 months for the encorafenib arm

^e Median follow-up at the latest data cut-off in COMBI-D (February 2016) was not reported, but should be longer than 20.0 months in the dabrafenib+trametinib arm and 16.0 months in the dabrafenib arm (the median follow-up at an earlier data cut-off January 2015).

^f Median duration of follow-up in COMBI-V was 23 months in the dabrafenib+trametinib arm. Duration of follow-up in the vemurafenib arm was not reported (data cut-off July 2016).

Source: Table compiled during evaluation, based on Sections 2.2-2.4 of the submission.

6.14 For the indirect comparison, a BRAF inhibitor was selected as the common reference, and treatment effects observed in COMBI-V and COMBI-D for dabrafenib+trametinib were pooled via a meta-analysis.

6.15 There are key transitivity concerns between the trials included in the indirect comparison.

- A lower proportion of patients in COLUMBUS had elevated lactate dehydrogenase level at baseline than in other trials (28% vs 33%-45%);
- The median duration of follow-up varied across trials (19 to 30 months);
- Cross-over from monotherapy to combination therapy was allowed in the two dabrafenib+trametinib trials (COMBI-D (12%) and COMBI-V (10%)), but not in COLUMBUS or coBRIM;
- Patients and investigators were blinded to treatment allocation in COMBI-D and coBRIM, as opposed to the open-label design of Trials COLUMBUS and COMBI-V.

The ESC considered that the overall impact of these differences on the results of indirect comparisons was unclear, but noted that similar issues were previously accepted in the consideration of vemurafenib+cobimetinib.

Comparative effectiveness

6.16 The results for PFS and OS in COLUMBUS Part 1 are summarised below.

Table 4: Results of PFS for encorafenib+binimetinib vs. vemurafenib vs. encorafenib (COLUMBUS Part 1)^a

	Combo 450 (E+B) N = 192	Vemurafenib (V) N = 191	Encorafenib (E) N = 194	E+B vs. V Stratified HR (95% CI) p-value (1-side)	E+B vs. E Stratified HR (95% CI) p-value (1-side)
Data cut-off 19 May 2016^b (primary analysis)					
Patients with events (%)	98/192 (51.0%)	106/191 (55.5%)	96/194 (49.5%)	–	–
Median PFS, months (95% CI)	14.9 (11.0, 18.5)	7.3 (5.6, 8.2)	9.6 (7.5, 14.8)	0.54 (0.41, 0.71) p<0.0001	0.75 (0.56, 1.00) p=0.0256
Data cut-off 7 November 2017^c (updated analysis)					
Patients with events (%)	113/192 (58.9%)	118/191 (61.8%)	112/194 (57.7%)	–	–
Median PFS, months (95% CI)	14.9 (11.0, 20.2)	7.3 (5.6, 7.9)	9.6 (7.4, 14.8)	0.51 (0.39, 0.67) p<0.0001	0.77 (0.59, 1.00) p=0.0249

B = binimetinib; CI = confidence interval; E = encorafenib; HR = hazard ratio; PFS = progression-free survival; V = vemurafenib

^a Method: full analysis set. Blinded Independent Review Committee (BIRC)-assessed tumour response. A Cox regression model stratified by randomisation stratification factors (cancer stage and performance status) was used to estimate the HR of PFS, along with 95% CI based on the Wald test. The p-values were one-sided and were based on the stratified log-rank test.

^b Median duration of follow-up: 14.9 months in the Combo 450 arm vs 7.3 months in the vemurafenib vs 9.6 months in the encorafenib arm.

^c Median duration of follow-up: 30.0 months in the Combo 450 arm vs 15.8 months in the vemurafenib vs 20.3 months in the encorafenib arm.

Source: Table compiled during the evaluation, based on Table 2.33, p89, Figure 2.4, p89, Figure 2.5, p90, Table 2.37, p96, Figure 2.38, p97 of the submission; Table 14.2-1.2a, p6 of COLUMBUS Part 1 efficacy update .

Table 5: Results of OS for encorafenib+binimetinib vs. vemurafenib vs. encorafenib (COLUMBUS Part 1)^a

	Combo 450 (E+B) N = 192	Vemurafenib (V) N = 191	Encorafenib (E) N = 194	E+B vs. V Stratified HR (95% CI) p-value	E+B vs. E Stratified HR (95% CI) p-value
Data cut-off 7 November 2017^b (interim analysis)					
Patients with events (%)	105/192 (54.7%)	127/191 (66.5%)	106/194 (54.6%)	–	–
Median OS, months (95% CI)	33.6 (24.4, 39.2)	16.9 (14.0, 24.5)	23.5 (19.6, 33.6)	0.61 (0.47, 0.79) p< 0.001	0.81 (0.61, 1.06) p=0.0613

B = binimetinib; CI = confidence interval; E = encorafenib; HR = hazard ratio; OS = overall survival; V = vemurafenib

^a Method: full analysis set. A Cox regression model stratified by randomisation stratification factors (cancer stage and performance status) was used to estimate the HR of OS, along with 95% CI based on the Wald test. The p-values were based on the log-rank test.

^b Median duration of follow-up: 30.0 months in the Combo 450 arm vs 15.8 months in the vemurafenib vs 20.3 months in the encorafenib arm

Source: Table compiled during the evaluation, based on Table 2.41, p102 of the submission; Table 4-4, p16 of COLUMBUS Part 1 OS topline report.

6.17 Encorafenib+binimetinib Combo 450 demonstrated a statistically significant reduction in the risk of progression and the risk of death compared with vemurafenib monotherapy. However, compared with encorafenib monotherapy, the differences did not reach statistical significance threshold specified in the protocol for either PFS (for primary analysis at data cut-off May 2016) or OS.

6.18 The results of the indirect comparisons of encorafenib+binimetinib with dabrafenib+trametinib and with vemurafenib+cobimetinib are summarised below.

Table 6: Comparison of median PFS and OS across trials

Trial	Combination therapy	BRAF inhibitor	Absolute difference
Median PFS			
COLUMBUS ^a Encorafenib+binimetinib vs. vemurafenib	14.9 months	7.3 months	7.6 months
COMBI-D ^b Dabrafenib+trametinib vs. dabrafenib	11.0 months	8.8 months	2.2 months
COMBI-V ^c Dabrafenib+trametinib vs. vemurafenib	12.1 months	7.3 months	4.8 months
coBRIM ^d Vemurafenib+cobimetinib vs. vemurafenib	12.3 months	7.2 months	5.1 months
Median OS			
COLUMBUS ^a Encorafenib+binimetinib vs. vemurafenib	33.6 months	16.9 months	16.7 months
COMBI-D ^b Dabrafenib+trametinib vs. dabrafenib	25.1 months	18.7 months	6.4 months
COMBI-V ^c Dabrafenib+trametinib vs. vemurafenib	26.1 months	17.8 months	8.3 months
coBRIM ^e Vemurafenib+cobimetinib vs. vemurafenib	22.3 months	17.4 months	4.9 months

OS = overall survival; PFS = progression-free survival

^a At data cut-off November 2017 in COLUMBUS Part 1. Median follow-up: 30.0 months in the Combo 450 arm vs 15.8 months in the vemurafenib.

^b At data cut-off January 2015 in COMBI-D. Median follow-up: 20.0 months in the dabrafenib+trametinib arm vs 16.0 months in the dabrafenib arm.

^c At data cut-off July 2016 in COMBI-V. Median follow-up: 23 months in the dabrafenib+trametinib arm. Duration of follow-up in the vemurafenib arm was not reported.

^d At data cut-off January 2015 in coBRIM. Median follow-up: 14.2 months in the overall population.

^e At data cut-off August 2015 in coBRIM. Median follow-up: 18.5 months in the overall population.

Source: Table compiled during the evaluation, based on Figure 2.5, p90, Table 2.48, p118, Figure 2.23, p115, Figure 2.33, p123, Table 2.71, p150 of the submission

Source: Table compiled during the evaluation, based on Figure 2.5, p90, Table 2.48, p118, Figure 2.23, p115, Figure 2.33, p123, Table 2.71, p150 of the submission

Table 7: Indirect comparison of overall survival

	Trial ID	Combination therapy, n/N (%)	BRAF inhibitor, n/N (%)	Treatment effect, HR (95% CI)
E+B vs. V	COLUMBUS ^a	105/192 (54.7%)	127/191 (66.5%)	0.61 (0.47, 0.79)
D+T vs. D or V	Pooled ^b	–	–	0.71 (0.60, 0.82)
	COMBI-D ^c	NR/211	NR/212	0.75 (0.58, 0.96)
	COMBI-V ^d	190/352 (53.8%)	218/352 (61.9%)	0.68 (0.56, 0.83)
Adjusted indirect estimate of effect for encorafenib+binimetinib vs dabrafenib+trametinib				0.86 (0.64, 1.17)
E+B vs. V	COLUMBUS ^a	105/192 (54.7%)	127/191 (66.5%)	0.61 (0.47, 0.79)
V+C vs. V	coBRIM ^e	114/247 (46.2%)	141/248 (56.9%)	0.70 (0.55, 0.90)
Adjusted indirect estimate of effect for encorafenib+binimetinib vs vemurafenib+cobimetinib				0.87 (0.61, 1.25)
Adjusted indirect estimate of effect for vemurafenib+cobimetinib vs dabrafenib+trametinib ^f				1.03 (0.77, 1.38)

CI = confidence interval; D = dabrafenib; D+T = dabrafenib+trametinib; E+B = encorafenib+binimetinib; HR = hazard ratio; NR = not reported; V = vemurafenib; V+C = vemurafenib+cobimetinib

^a At data cut-off November 2017 in COLUMBUS Part 1. Median follow-up: 30.0 months in the Combo 450 arm vs 15.8 months in the vemurafenib.

^b Pooled HR was calculated using fixed effects meta-analysis methodology described by Neyeloff et al.

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^c At data cut-off February 2016 in COMBI-D. Median follow-up at this cut-off was not reported, but should be longer than 20.0 months in the dabrafenib+trametinib arm and 16.0 months in the dabrafenib arm (median follow-up at an earlier data cut-off January 2015).

^d At data cut-off July 2016 in COMBI-V. Median follow-up: 23 months in the dabrafenib+trametinib arm. Duration of follow-up in the vemurafenib arm was not reported.

^e At data cut-off August 2015 in coBRIM. Median follow-up: 18.5 months in the overall population.

^f Provided in the PSCR, Table 1, p5

Source: Table compiled during the evaluation, based on Table 2.69, p149, Table 2.41, p102, Figure 2.34, p124 of the submission; p5 of Robert et al 2016.

Table 8: Indirect comparison of progression-free survival (investigator assessed)

	Trial ID	Combination therapy, n/N (%)	BRAF inhibitor, n/N (%)	Treatment effect, HR (95% CI)
E+B vs. V	COLUMBUS ^a	117/192 (60.9%)	136/191 (71.2%)	0.47 (0.36, 0.60)
	Pooled ^b	–	–	0.65 (0.56, 0.74)
D+T vs. D or V	COMBI-D ^c	NR/211	NR/212	0.71 (0.57, 0.88)
	COMBI-V ^d	NR/352	NR/352	0.61 (0.51, 0.73)
Adjusted indirect estimate of effect for encorafenib+binimetinib vs dabrafenib+trametinib				0.72 (0.54, 0.97)
E+B vs. V	COLUMBUS ^a	117/192 (60.9%)	136/191 (71.2%)	0.47 (0.36, 0.60)
V+C vs. V	coBRIM ^e	143/247 (57.9%)	180/248 (72.6%)	0.58 (0.46, 0.72)
Adjusted indirect estimate of effect for encorafenib+binimetinib vs vemurafenib+cobimetinib				0.81 (0.58, 1.14)
Adjusted indirect estimate of effect for vemurafenib+cobimetinib vs dabrafenib+trametinib ^f				0.92 (0.71, 1.20)

CI = confidence interval; D = dabrafenib; D+T = dabrafenib+trametinib; E+B = encorafenib+binimetinib; HR = hazard ratio; NR = not reported; V = vemurafenib; V+C = vemurafenib+cobimetinib

^a At data cut-off November 2017 in COLUMBUS Part 1. Median follow-up: 30.0 months in the Combo 450 arm vs 15.8 months in the vemurafenib.

^b Pooled HR was calculated using fixed effects meta-analysis methodology described by Neyeloff et al.

^c At data cut-off February 2016 in COMBI-D. Median follow-up at this cut-off was not reported, but should be longer than 20.0 months in the dabrafenib+trametinib arm and 16.0 months in the dabrafenib arm (median follow-up at an earlier data cut-off January 2015).

^d At data cut-off July 2016 in COMBI-V. Median follow-up: 23 months in the dabrafenib+trametinib arm. Duration of follow-up in the vemurafenib arm was not reported.

^e At data cut-off January 2015 in coBRIM. Median follow-up: 14.2 months in the overall population.

^f Provided in the PSCR, Table 1, p5

Source: Table compiled during the evaluation, based on Table 2.72, p151, Figure 2.7, p93, Figure 2.33, p123 of the submission.

6.19 The hazard ratio (HR) for PFS and OS from the indirect comparisons numerically favoured encorafenib+binimetinib, compared with dabrafenib+trametinib and with vemurafenib+cobimetinib. The differences did not reach statistical significance except PFS for encorafenib+binimetinib versus dabrafenib+trametinib. The submission did not establish non-inferiority margins or minimal clinically important differences for the outcomes. It is unclear whether the 95% CIs from the indirect comparisons included a clinically important difference.

6.20 Given the transitivity issues, the evaluation considered that comparative treatment effects generated from indirect comparisons of encorafenib+binimetinib with dabrafenib+trametinib and encorafenib+binimetinib with vemurafenib+cobimetinib could be biased and should be interpreted with caution.

Comparative harms

6.21 The key safety data observed from COLUMBUS PART 1 are summarised below.

Table 9: Summary of deaths and adverse events in COLUMBUS Part 1 (7 November 2017 cut-off)^a

	Combo 450 (E+B) N = 192		Vemurafenib N = 186		Encorafenib N = 192	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
On-treatment deaths ^b	23 (12.0%)	–	20 (10.8%)	–	16 (8.3%)	–
Any AEs	189 (98.4%)	123 (64.1%)	186 (100%)	122 (65.6%)	191 (99.5%)	129 (67.2%)
Serious AEs	74 (38.5%)	65 (33.9%)	75 (40.3%)	63 (33.9%)	69 (35.9%)	58 (30.2%)
AEs leading to discontinuation	29 (15.1%)	24 (12.5%)	32 (17.2%)	19 (10.2%)	29 (15.1%)	22 (11.5%)
AEs requiring dose interruption/adjustment	102 (53.1%)	67 (34.9%)	115 (61.8%)	72 (38.7%)	137 (71.4%)	88 (45.8%)
AEs requiring additional therapy ^c	170 (88.5%)	80 (41.7%)	173 (93.0%)	94 (50.5%)	182 (94.8%)	107 (55.7%)

AE = adverse event; B = binimetinib; E = encorafenib

^a Median duration of exposure: 51.2 weeks in the Combo 450 arm vs 26.3 weeks in the vemurafenib arm vs 31.4 weeks in the encorafenib arm

^b Deaths occurring >30 days after end of treatment are not included.

^c Additional therapy includes all non-drug therapy and concomitant medications.

Source: Table 2.54, p128 of the submission.

6.22 In patients receiving encorafenib+binimetinib, the most frequently reported Grade 3 or 4 AEs were elevated gamma-glutamyl transferase (9.4%), hypertension (6.3%), elevated alanine aminotransferase (5.2%) and anaemia (4.7%). With regards of AEs of special interest (AESIs), patients in the combination therapy arm were less likely to experience some AEs associated with key BRAF-inhibitor class effects, such as rash, myopathy, alopecia, cutaneous squamous cell carcinoma, tachycardia and facial paresis, compared with those in the vemurafenib group. The addition of binimetinib to encorafenib added toxicity due to MEK-inhibitor class effects, including AESIs of retinopathy excluding retinal vein occlusion, liver function test abnormalities, muscle enzyme/protein changes, haemorrhage, hypertension and left ventricular dysfunction. The PSCR (p3) maintained encorafenib + binimetinib has demonstrated an acceptable safety profile. The ESC considered that the available clinical data indicated a safety profile consistent with those reported for the other BRAF/MEK inhibitor combination treatments.

6.23 The submission conducted indirect comparisons of safety outcomes. The indirect estimates of comparative safety, in terms of overall AEs, Grade 3-5 AEs and AEs leading to discontinuation, numerically favoured encorafenib+binimetinib over the other two targeted combination therapies, except Grade ≥3 AEs for encorafenib+binimetinib versus dabrafenib+trametinib. However, it is noted that assessment of safety outcomes could have been biased (likely in favour of combination therapies), especially in the two open-label trials of COLUMBUS and COMBI-V.

6.24 The evaluation considered that the indirect comparisons of safety outcomes were difficult to interpret due to concerns regarding the transitivity of the trials. The

evaluation considered these concerns contributed to different event rates between the common references groups, e.g. AE-related discontinuation in the BRAF inhibitor arms were 17.2% in COLUMBUS vs 6.6% in COMBI-D vs 15.5% in COMBI-V vs 6.9% in coBRIM.

- 6.25 Based on the data presented in the submission, a comparison of AESIs across encorafenib+binimetinib, dabrafenib+trametinib and vemurafenib+cobimetinib could not be undertaken. It is likely that the safety profiles of different combination therapies differ in terms of AESI type and/or incidence, in particular AEs being driven by binimetinib, and these may impact upon patient quality of life differently and require different treatments.

Clinical claim

- 6.26 The submission described encorafenib+binimetinib as at least non-inferior in terms of effectiveness and safety compared with dabrafenib+trametinib and vemurafenib+cobimetinib.
- 6.27 The ESC noted that there was uncertainty regarding the non-inferiority claim of encorafenib+binimetinib relative to dabrafenib+trametinib and vemurafenib+cobimetinib, both in terms of effectiveness and safety as:
- This claim relied on common reference-adjusted indirect comparisons of the COLUMBUS, COMBI-V, COMBI-D and coBRIM trials. The data were derived from different trial populations and settings which could have invalidated the transitivity assumption.
 - The submission did not present non-inferiority margins or clinically justified minimum clinically important differences for the outcomes. The indirect point estimates favoured encorafenib+binimetinib for all comparison of OS, PFS, overall AEs, Grade 3-5 AEs and discontinuation, with the exception of Grade ≥ 3 AEs versus dabrafenib+trametinib. However, clinically meaningful worsening of these endpoints could not be ruled out based on the confidence intervals from the indirect comparisons.
- 6.28 The PBAC accepted the claim of non-inferior comparative effectiveness. The Committee noted the absence of an appropriate non-inferiority margin and the variability of the results of the indirect comparison, but recalled that it had accepted similar issues in its consideration of vemurafenib+cobimetinib in March 2016.
- 6.29 The PBAC concluded that the claim of non-inferior safety was supported and that overall, the safety profile of encorafenib+binimetinib was considered to be broadly consistent with dabrafenib+trametinib and vemurafenib+cobimetinib. However, it noted significant hypertension, left ventricular dysfunction, venous thromboembolism, haemorrhage, and rhabdomyolysis was associated with encorafenib+binimetinib.

Economic analysis

- 6.30 The submission presented a cost-minimisation analysis based on the indirect comparisons of encorafenib+binimetinib with dabrafenib+trametinib and with vemurafenib+cobimetinib. The ESC considered that a cost-minimisation analysis was appropriate.
- 6.31 The submission's proposed equi-effective doses for encorafenib+binimetinib versus dabrafenib+trametinib and versus vemurafenib+cobimetinib were:
- Encorafenib 450 mg once daily + binimetinib 45 mg twice daily, and
 - Dabrafenib 150 mg twice daily + trametinib 2 mg once daily, or
 - Vemurafenib 960 mg twice daily + cobimetinib 60 mg once daily (21 days on-treatment plus 7 days off-treatment, in a 28-day cycle).
- 6.32 The equi-effective doses were sourced from the four clinical trials included in the indirect comparisons and are consistent with the recommended doses in the respective Product Information documents. The ESC considered that the equi-effective doses were reasonable.
- 6.33 The submission's cost-minimisation analysis was performed on the basis of daily ex-manufacturer prices of targeted combination therapies and reflected different periods of supply and was based on the published prices of the comparators (see Table 10). The PBAC noted these would need to be updated based on the effective prices.

Table 10: Results of the cost-minimisation analysis

	Encorafenib+binimetinib		Dabrafenib+trametinib		Vemurafenib cobimetinib	
	Encorafenib	Binimetinib	Dabrafenib	Trametinib	Vemurafenib	Cobimetinib
Dose regimen	450 mg once daily	45 mg twice daily	150 mg twice daily	2 mg once daily	960 mg twice daily	60 mg once daily (21/28 days)
Drug strength, form	75 mg, capsule	15 mg, tablet	75 mg, capsule	2 mg, tablet	240 mg, tablet	20 mg, tablet
No. units per day	6	6	4	1	8	2.25 ^a
Submission's analysis (on an ex-manufacturer price basis)						
Ex-manufacturer price for maximum quantity	\$8,038.04	\$8,038.04	\$8,612.17	\$8,612.17	\$8,038.04	\$8,038.03
Maximum quantity	168	168	120	30	224	63
Ex-manufacturer price/unit	\$47.85	\$47.85	\$71.77	\$287.07	\$35.88	\$127.59
Cost per day	\$287.07	\$287.07	\$287.07	\$287.07	\$287.07	\$287.07
Cost of combination therapy per day	\$574.15		\$574.15		\$574.15	

^a = 60/20*21/28, where 60 is the mg per day for cobimetinib; 20 is the tablet strength; 21 is the days on treatment per treatment cycle; and 28 is the cycle length.

Source: Adapted from Table 3.3, p166 of the submission.

- 6.34 The cost per day for encorafenib+binimetinib combination therapy (\$574.15) is identical to that of vemurafenib+cobimetinib and dabrafenib+trametinib.
- 6.35 Costs for the management of AEs were not included in the economic analysis. Combination therapies have different AEs profiles. The AE-related costs vary as individual AEs have different impacts upon the quality of life of patients and require

different treatments. On this basis, the evaluation considered that not including AE-related costs in the economic analysis was not adequately justified in the submission. The ESC considered that adverse events were broadly similar across all BRAF/MEK inhibitor combination treatments.

Drug cost/patient/28-day treatment: \$16,378

- 6.36 The estimated dispensed cost per patient per 28 days of treatment with encorafenib+binimetinib was \$16,378, based on an ex-manufacturer price of \$8,038 both for the maximum quantity of encorafenib (75mg x 168 capsules) and for the maximum quantity of binimetinib (15mg x 168 tablets) as per cost-minimisation analysis (Table 10), taking into account the updated mark-ups and dispensing fee.
- 6.37 The dispensed costs per patient per 28 days of treatment with dabrafenib+trametinib and vemurafenib+cobimetinib were \$16,358 and \$16,378, respectively.

Estimated PBS usage & financial implications

- 6.38 This submission was not considered by DUSC. The submission used a market-share approach to estimate the financial impacts related to the proposed listing of encorafenib+binimetinib in the first six years of listing. The ESC considered this was appropriate, as the market of targeted therapies was not expected to grow due to the listing of encorafenib+binimetinib.
- 6.39 The table below provides a summary of the estimated use of encorafenib+binimetinib and the estimated net cost to the PBS/RPBS, based on the published price of dabrafenib+trametinib and vemurafenib+cobimetinib.

The redacted table shows that at year 6, the estimated number of scripts was less than 10,000 per year.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed						
Estimated financial implications of encorafenib+binimetinib						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	\$	\$	\$	\$	\$	\$
Total cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
<i>Revised^a</i>						
Estimated financial implications for dabrafenib+trametinib and vemurafenib+cobimetinib						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	\$	\$	\$	\$	\$	\$
Total cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Net financial implications						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
<i>Revised^a</i>						
Net cost to MBS	\$0	\$0	\$0	\$0	\$0	\$0

^a Revised by correcting the submission's referencing error in calculating the net cost of binimetinib to the PBS/RPBS.

Source: Table 4.5, p180, Table 4.7, p182, Table 4.8, p182, Table 4.9, p182, Table 4.12, p184, Table 4.15, p187 of the submission.

- 6.40 The submission estimated that the listing of encorafenib+binimetinib combination therapy would result in an additional cost of approximately \$less than \$10 million per year over the first six years of listing.
- 6.41 The major financial uncertainty was the uptake of encorafenib+binimetinib (submission's assumption: ■% in Year 1, increasing to ■% in Years 5-6). The uptake rate however, would not have a substantial impact on the calculated net cost to the PBS/RPBS, given the cost-minimisation analysis approach taken by the submission.
- 6.42 The PSCR (p4) requested that if recommended, a Special Pricing Arrangement (SPA) would apply to the listing of encorafenib + binimetinib, in-line with the effective prices of dabrafenib+trametinib and vemurafenib+cobimetinib.

Quality Use of Medicines

- 6.43 The submission did not identify any quality use of medicines (QUM) issues. One QUM concern related to the use of encorafenib+binimetinib identified during evaluation is its increased pill burden compared with dabrafenib+trametinib (12 tablets/capsules per day vs. 5 tablets/capsules per day).

Financial Management – Risk Sharing Arrangements

- 6.44 No Risk Share Arrangement (RSA) was proposed in the submission. It is noted that there is a RSA between the sponsors of comparator combination therapies, dabrafenib+trametinib and vemurafenib+cobimetinib, and the Department.

For more details on the PBAC's view, see Section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of encorafenib in combination with binimetinib, for the treatment of BRAF V600 mutation positive unresectable Stage III or Stage IV metastatic melanoma, on a cost-minimisation basis against dabrafenib+trametinib and vemurafenib+cobimetinib.
- 7.2 The PBAC acknowledged the input provided by individuals, health care professionals and organisations describing the clinical benefits and consumer demand for encorafenib+binimetinib in patients with BRAF V600 mutation-positive cutaneous melanoma.
- 7.3 The PBAC considered that the regimens of dabrafenib+trametinib and vemurafenib+cobimetinib were the appropriate comparators for the combination of encorafenib+binimetinib.
- 7.4 The PBAC considered that the equi-effective doses were encorafenib 450 mg once daily + binimetinib 45 mg twice daily or dabrafenib 150 mg twice daily + trametinib 2 mg once daily or vemurafenib 960 mg twice daily + cobimetinib 60 mg once daily (21

days on-treatment plus 7 days off-treatment, in a 28-day cycle).

- 7.5 The PBAC accepted the clinical non-inferiority of encorafenib+binimetinib versus dabrafenib+trametinib and vemurafenib+cobimetinib, but noted the absence of an appropriate non-inferiority margin and the variability of the results of the indirect comparison.
- 7.6 The PBAC accepted the claim of non-inferior comparative safety between encorafenib+binimetinib and dabrafenib+trametinib and vemurafenib+cobimetinib. The PBAC considered that the safety profiles were broadly consistent, noting the significant hypertension, left ventricular dysfunction, venous thromboembolism, haemorrhage and rhabdomyolysis associated with encorafenib+binimetinib.
- 7.7 The PBAC accepted the cost-minimisation analysis and the financial impact estimates, and considered that the costs of managing adverse events would be similar between encorafenib+binimetinib and the comparator combination therapies.
- 7.8 The PBAC noted that the sponsor of encorafenib+binimetinib would be required to enter Deeds of Agreement to share the current RSA Subsidisation Caps in place with the sponsors of dabrafenib+trametinib and vemurafenib+cobimetinib, applying the same rebate above the Cap should this be exceeded, to ensure no additional cost to Government beyond current Subsidisation caps.
- 7.9 The PBAC accepted the proposed restriction noting it was consistent with restrictions for the comparator combination regimens. The PBAC noted there would be separate listings for encorafenib and binimetinib that exclude monotherapy.
- 7.10 The PBAC advised that there are no drugs or medicinal preparations that should be treated as interchangeable with encorafenib+binimetinib on an individual patient basis.
- 7.11 The PBAC advised that the combination of encorafenib+binimetinib is not suitable for prescribing by nurse practitioners.
- 7.12 The PBAC recommended that the Early Supply Rule should not apply.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review as it was a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item

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Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Proprietary Name and Manufacturer	
ENCORAFENIB				
50 mg capsule, 28	9	3	BRAFTOVI	Pierre Fabre
75 mg capsule, 42	4	3		

Category / Program:	General Schedule
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The condition must be positive for a BRAF V600 mutation, AND Patient must be receiving PBS-subsidised binimetinib concomitantly for this condition; AND The condition must not have been treated previously with PBS subsidised therapy; OR Patient must have developed intolerance to another BRAF inhibitor of a severity necessitating permanent treatment withdrawal, AND Patient must have a WHO performance status of 2 or less.</p>
Administrative Advice:	<p>A patient who has had progressive disease when treated with another BRAF inhibitor is not eligible to receive PBS-subsidised treatment with this drug.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply</p>

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Proprietary Name and Manufacturer	
ENCORAFENIB				
50 mg capsule, 28	9	5	BRAFTOVI	Pierre Fabre
75 mg capsule, 42	4	5		

Category / Program:	General Schedule
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Continuing treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

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Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug, AND Patient must be receiving PBS-subsidised binimetinib concomitantly for this condition; AND Patient must have stable or responding disease
Administrative Advice:	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug A patient who has had progressive disease when treated with another BRAF inhibitor is not eligible to receive PBS-subsidised treatment with this drug. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Proprietary Name and Manufacturer	
BINIMETINIB 15 mg capsule, 84	2	3	MEKTOVI	Pierre Fabre
Category / Program:	General Schedule			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Severity:	Unresectable Stage III or Stage IV			
Condition:	Malignant melanoma			
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma			
Treatment phase:	Initial treatment			
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined			
Clinical criteria:	Patient must be receiving PBS-subsidised encorafenib concomitantly for this condition; AND Patient must not have had progressive disease when treated with a BRAF inhibitor.			
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply			

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Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Proprietary Name and Manufacturer	
BINIMETINIB 15 mg capsule, 84	2	5	MEKTOVI	Pierre Fabre
Category / Program:	General Schedule			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Severity:	Unresectable Stage III or Stage IV			
Condition:	Malignant melanoma			
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma			
Treatment phase:	Continuing treatment			
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined			
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug, AND Patient must be receiving PBS-subsidised encorafenib concomitantly for this condition, AND Patient must have stable or responding disease			
Administrative Advice:	A patient who has had progressive disease when treated with this drug is no longer eligible for PBS subsidised treatment with this drug. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply			

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Pierre Fabre welcomes the PBAC's recommendation to make Braftovi® (encorafenib) with Mektovi® (binimetinib) available for use in combination for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.