

## 5.01 VEMURAFENIB, tablet 240 mg, Zelboraf® + COBIMETINIB, tablet 20 mg, Cotellic®, Roche Products Pty Ltd

### 1 Purpose of Application

- 1.1 Authority Required (streamlined) listing for vemurafenib in combination with cobimetinib for the treatment of *BRAF* V600 mutation positive unresectable or metastatic melanoma.

### 2 Requested listing

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

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
VEMURAFENIB 240 mg tablet, 56	4	3	\$ [REDACTED]	ZELBORAF Roche Products Pty Limited

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	The condition must be positive for a <i>BRAF</i> V600 mutation, AND Patient must be receiving PBS subsidised cobimetinib 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 <i>BRAF</i> inhibitor of a severity necessitating permanent treatment withdrawal, AND Patient must have a WHO performance status of 2 or less.

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<b>Administrative Advice</b>	<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>
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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
VEMURAFENIB 240 mg tablet, 56	4	5	\$ [REDACTED]	ZELBORAF Roche Products Pty Limited

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	<p>Patient must have previously been issued with an authority prescription for this drug, AND</p> <p>Patient must have stable or responding disease.</p>
<b>Administrative Advice</b>	<p>A patient who has had progressive disease when treated with this drug is no longer eligible for 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	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
COBIMETINIB 20 mg tablet, 63	1	3	\$ [REDACTED]	COTELLIC Roche Products Pty Limited

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<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	Patient must be receiving PBS subsidised vemurafenib concomitantly for this condition, AND Patient must not have had progressive disease when treated with a <i>BRAF</i> inhibitor.
<b>Administrative Advice</b>	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	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
COBIMETINIB 20 mg tablet, 63	1	5	\$ [REDACTED]	COTELLIC Roche Products Pty Limited

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	Patient must have previously been issued with an authority prescription for this drug, AND Patient must be receiving PBS-subsidised vemurafenib concomitantly for this condition, AND Patient must have stable or responding disease.
<b>Administrative Advice</b>	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 The requested listing of vemurafenib + cobimetinib administered concomitantly is based on cost-minimisation analysis compared with dabrafenib + trametinib administered concomitantly.
- 2.3 On a pragmatic basis, the listing of vemurafenib + cobimetinib was also requested to follow progression on immunotherapy, in the event that immunotherapies are PBS-listed for previously untreated *BRAF* V600 positive patients.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”.*

### 3 Background

- 3.1 An application was filed with the TGA in May 2015 for the use of cobimetinib in combination with vemurafenib, for the treatment of patients with *BRAF* V600 mutation

positive unresectable or metastatic melanoma. The TGA delegate's overview was available at the time of PBAC for consideration. The overview indicated that consideration at the ACPM meeting in April 2016 was not required to register cobimetinib.

- 3.2 This was the first consideration by the PBAC of vemurafenib + cobimetinib for the treatment of *BRAF* V600 mutation positive unresectable or metastatic melanoma.
- 3.3 Two previous submissions for vemurafenib monotherapy treatment of unresectable or metastatic melanoma were deferred by the PBAC in July 2012 and March 2013.
- 3.4 A coordinated application to MSAC to request an amendment to include vemurafenib in the existing MBS item descriptor (73336) for *BRAF* testing is being undertaken by the sponsor.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

#### **4 Clinical place for the proposed therapy**

- 4.1 The submission placed vemurafenib + cobimetinib as a first-line treatment option for *BRAF* positive patients alongside dabrafenib + trametinib. The PBAC accepted this positioning.
- 4.2 The submission presented an alternative treatment algorithm in which first-line treatment for *BRAF* positive patients includes PD-1 inhibitors, BRAF + MEK inhibitors along with nivolumab + ipilimumab, and best supportive care. The PBAC did not accept this alternative treatment algorithm.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

#### **5 Comparator**

- 5.1 The nominated comparator was combination therapy with dabrafenib + trametinib. This is the appropriate comparator given the current treatment algorithm, although this algorithm is still evolving. The submission did not consider a secondary comparison against the PD-1 inhibitors, nivolumab or pembrolizumab, but in its Section F, the submission also requested a modification to the proposed listing which would put vemurafenib + cobimetinib alongside PD-1 inhibitors as a first-line treatment option for *BRAF* mutation positive patients. ESC advised that the main clinical uncertainty with the immunotherapies related to the sequencing of genetically targeted treatment and immunotherapy. The PBAC rejected the request for this additional restriction where the combination of BRAF/MEK inhibitors follows PD1 inhibitors.

*For more detail on 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 that no consumer comments were received for this item.

**Clinical trials**

6.3 With no head-to-head trials comparing vemurafenib + cobimetinib to dabrafenib + trametinib, the submission was based on an indirect comparison using the coBRIM trial for vemurafenib + cobimetinib (n=495) and the COMBI-D (n=225) and COMBI-V (n=310) trials for dabrafenib + trametinib.

6.4 Details of the trials presented in the submission are provided in Table 1 below.

**Table 1: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation	Comparable
<b>Vemurafenib + cobimetinib trial</b>			
coBRIM	Clinical study report GO28141 – A Phase III double-blind, placebo controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated <i>BRAF</i> 600-mutation positive patients with unresectable locally advanced or metastatic melanoma.	Genentech Inc November 2014	Yes
	Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in <i>BRAF</i> -mutated melanoma	NEJM 2014; 371(20):1867-76	
	Larkin J, Yan Y, McArthur GA et al. Update of progression-free survival (PFS) and correlative biomarker analysis from coBRIM: Phase III study of cobimetinib (cobi) plus vemurafenib (vem) in advanced <i>BRAF</i> -mutated melanoma.	J Clin Oncol 33, 2015 (suppl; abstr 9006)	
<b>Dabrafenib + trametinib trials</b>			
COMBI-D	Clinical study protocol - 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) <i>BRAF</i> V600E/K mutation-positive cutaneous melanoma.	GSK February 2012	Yes
	Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma.	NEJM 2014; 371(20):1877-88	
	Long GV, Stroyakovskiy DL et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 <i>BRAF</i> -mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial.	The Lancet 2015; 386: 444–51	
	Long GV, Stroyakovskiy DL. COMBI-d: A randomized, double-blinded, Phase III study comparing the combination of dabrafenib and trametinib to dabrafenib and trametinib placebo as first-line therapy in patients (pts) with unresectable or metastatic <i>BRAF</i> V600E/K mutation-positive cutaneous melanoma	J Clin Oncol 32:5s, 2014 (suppl; abstr 9011)	
COMBI-V	Clinical study protocol - 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) <i>BRAF</i> V600E/K mutation-positive cutaneous melanoma.	GSK March 2012	Yes
	Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib.	NEJM 2015; 372(1):30-9	
	Grob JJ, Amonkar M et al. COMBI-v: health-related quality of life (HRQoL) impact of the combination of dabrafenib and trametinib (D+T) vs vemurafenib (V) in patients with <i>BRAF</i> V600 metastatic melanoma (MM).	European Cancer Congress 2015, (abstr 3345)	

Source: Table B.2.5 of Section B-ICRT of the submission and literature provided by the submission.

6.5 The key features of the randomised trials included in the indirect comparison are summarised in Table 2.

**Table 2: Key features of the included evidence**

Trial ID	Trial design /N	Primary outcome	Vemurafenib+cobimetinib	Common reference	Dabrafenib+trametinib	Risk of bias	Used in the CMA
<b>Proposed combination – vemurafenib + cobimetinib</b>							
CoBRIM <sup>a</sup>	R, DB, MC, phase III N=495	PFS	Vem 960 mg BD days 1-28 of each 28 day cycle + cobimetinib 60 mg QD days 1-21 of each cycle	Plb + vem 960 mg BD on days 1-28 of each 28 day cycle	NA	Low	Yes
<b>Main comparator – dabrafenib + trametinib</b>							
COMBI-D <sup>a</sup>	R, DB, MC, phase III N=423	PFS	NA	Plb + dabrafenib 150 mg BD	Dabra 150 mg BD + tram 2 mg QD	Low	Yes
COMBI-V	R, OL, MC, phase III N=704	OS	NA	Vem 960 mg BD	Dabra 150 mg BD + tram 2 mg QD	Low	Yes

Source: Table B.2.5, p7, Section B-ICRT of the submission and related text.

<sup>a</sup> cross-over not permitted

BD=twice daily; CMA=cost-minimisation analysis; cobimetinib; dabrafenib; DB=double-blind; MC=multi-centre; NA=not applicable; OL=open label; OS=overall survival; PFS=progression-free survival; plb=placebo; QD=once daily; R=randomised; tram=trametinib; vem=vemurafenib

- 6.6 While the dabrafenib + trametinib COMBI-V trial was open-label and therefore at some risk of bias, the objective nature of the outcomes plus the use of independent review minimised the impact of any such bias. The COMBI-V trial also allowed cross-over, which the submission acknowledged may bias results. The November 2014 PSD for trametinib (paragraph 6.5) identified COMBI-V as having a low risk of bias and while the possibility of cross-over may have favoured vemurafenib + cobimetinib, it is difficult to determine the potential impact of this on the results. The ESC noted that very few individuals switched to the combination in COMBI-V.
- 6.7 Although the risk of bias within each trial can be considered low, there was some potential for bias in the indirect comparison, given issues with exchangeability of the trials (see 'Comparative effectiveness below' for further detail).

### **Comparative effectiveness**

- 6.8 Table 3 provides the median PFS and OS results from each of the trials. Table 4 provides the results of the indirect comparison.

**Table 3: Median duration of PFS and OS in the trials included in the indirect comparison**

Trial	Combination therapy	BRAF inhibitor	Absolute difference
<b>Progression-free survival - median months</b>			
coBRIM	12.3	7.2	5.1 months
COMBI-D	11.0	8.8	2.2 months
COMBI-V	12.6	7.3	5.3 months
<b>Overall survival - median months</b>			
coBRIM	22.3	17.4	4.9 months
COMBI-D	25.1	18.7	6.4 months
COMBI-V	25.6	18.0	7.6 months

Source: compiled during the evaluation.

**Table 4: Indirect comparison - PFS and OS**

Trial	coBRIM: vemurafenib + cobimetinib			COMBI-D/COMBI-V: dabrafenib + trametinib			Indirect HR (95% CI)
	HR (95% CI)	Vem + cobi n/N <sup>a</sup> (%)	BRAF inhibitor n/N <sup>a</sup> (%)	BRAF inhibitor n/N <sup>a</sup> (%)	Dabra + tram n/N <sup>a</sup> (%)	HR (95% CI)	
<b>Progression-free survival</b>							
coBRIM	0.58 (0.46, 0.72)	143/247 (58%)	180/248 (73%)				
COMBI-D				162/212 (76%)	139/211 (66%)	0.67 (0.53, 0.84)	
COMBI-V				NR/352	NR/352	0.61 (0.51, 0.73)	
Pooled						0.63 (0.55, 0.73)	
<b>Indirect comparison – PFS</b>							0.92 (0.71, 1.20)
<b>Overall survival</b>							
coBRIM	0.70 (0.55, 0.90)	114/247 (46%)	141/248 (57%)				
COMBI-D				123/212 (58%)	99/211 (47%)	0.71 (0.55, 0.92)	
COMBI-V				218/352 (62%)	172/352 (49%)	0.66 (0.53, 0.81)	
Pooled				341/564 (60%)	271/563 (48%)	0.68 (0.58, 0.80)	
<b>Indirect comparison – OS</b>							1.03 (0.77, 1.38)

Source: Table B.6.1, p.31 and Table B.6.2, p34 of Section B-ICRT of the submission.

<sup>a</sup> n/N=Progressed or died/total N

cobi=cobimetinib; dabra=dabrafenib; HR=hazard ratio; NR=not reported; tram=trametinib; vem=vemurafenib

- 6.9 The results of the indirect comparison demonstrated no statistically significant difference between vemurafenib + cobimetinib and dabrafenib + trametinib for both PFS and OS.
- 6.10 The results of the indirect comparison were interpreted cautiously (see “clinical claim” below).

### Comparative harms

- 6.11 The submission provided detailed safety outcomes from the coBRIM, COMBI-D and COMBI-V trials, but did not provide any statistical comparisons of safety data given differences in outcomes measured across the trials and limited availability of safety data for the COMBI-D and COMBI-V trials. Table 5 below provides a summary of key adverse events for the combination therapy groups across the vemurafenib + cobimetinib trial and the two dabrafenib + trametinib trials.

**Table 5: Summary of adverse events in the vemurafenib + cobimetinib trial and the dabrafenib + trametinib trials**

Adverse event	coBRIM: vemurafenib + cobimetinib N=254	COMBI-D/COMBI-V: dabrafenib + trametinib N=559
Any AE	250 (98%)	542 (97%)
Treatment-related AEs	NR	498 (89%)
Grade ≥3 AEs <sup>a</sup>	165 (65%)	240 (43%)
Serious AEs <sup>b</sup>	75 (30%)	195 (35%)
Treatment-related serious AEs	46 <sup>c</sup> (18%) <sup>d</sup>	273 <sup>c</sup> (67%) <sup>d</sup>
AEs leading to discontinuation	49 (19%)	65 (12%)
AEs leading to dose modification	246 (97%)	261 (47%)
AEs leading to death	6 (2%)	6 (1%)
Treatment-related deaths	1 (<1%)	0 (0%)
Diarrhoea <sup>e</sup>	145 (57%)	162 (29%)

Source: Table B.6.12, p47 of Section B-ICRT of the submission.

<sup>a</sup> In coBRIM, AEs Grade ≥3 were reported if occurring in at least 2% of patients. In COMBI-D and COMBI-V, Grade ≥3 AEs that occurred in at least 10% of patients were reported.

<sup>b</sup> The protocol definition of serious adverse events differs across the coBRIM and COMBI trials. The specific events listed here occurred in ≥1% of patients.

<sup>c</sup> Number of serious AEs instead of number of patients with serious AEs

<sup>d</sup> Proportion of all serious AEs

<sup>e</sup> Patient numbers calculated during the evaluation from proportions of patients with diarrhoea provided in the submission.

AE=adverse event

6.12 The submission concluded that the safety profile of vemurafenib + cobimetinib, while different from that of dabrafenib + trametinib, is tolerable and manageable. The submission concluded that it was therefore not necessary to include the cost of AEs in the cost-minimisation analysis or the financial estimates. This conclusion though is by assertion and is not supported by quantitative evidence. The results summarised in the table above indicate the following:

- There was a much greater proportion of patients in the coBRIM trial with Grade ≥3 AEs (65%) than those in the COMBI-D and COMBI-V trials (43%). The submission notes that Grade ≥3 AEs were assessed differently across the trials - at least 2% of patients in coBRIM and at least 10% of patients in COMBI-D and COMBI-V. The submission suggested this comparison is likely to underestimate the toxicity of dabrafenib + trametinib. This cannot be determined without availability of the relevant data. The submission's discussion of treatment and management of Grade ≥3 AEs provided limited data and did not strongly support the assertion of no additional costs associated with the use of vemurafenib + cobimetinib.
- A greater proportion of patients in coBRIM discontinued treatment due to AEs (19%) compared to patients in COMBI-D and COMBI-V (12%). A greater proportion of patients in coBRIM (97%) experienced AEs leading to dose modification compared to patients in COMBI-D and COMBI-V (47%). These results reflect the potential impact of AEs on patient compliance with treatment. The submission did not provide any analyses of coBRIM data focusing on patients who discontinued treatment due to AEs or modified their dose - it would be informative to see what impact this had on the efficacy outcomes.

### **Clinical claim**

6.13 The submission described vemurafenib + cobimetinib as clinically non-inferior to dabrafenib + trametinib. In terms of comparative safety, the submission stated that

while the safety profile of vemurafenib + cobimetinib is different to dabrafenib + trametinib, the AE profile is manageable with no additional cost implications.

6.14 The claim of non-inferior comparative effectiveness was partially supported, for the following reasons:

- While the indirect comparisons demonstrated no statistically significant differences between vemurafenib + cobimetinib compared to dabrafenib and trametinib for PFS and OS, there was no discussion or establishment of an appropriate non-inferiority margin by the submission. Consideration of the applicability of a non-inferiority margin would have been beneficial, particularly given the variability in the indirect comparison results, where the OS results favoured dabrafenib + trametinib.
- Results of the indirect comparisons revealed a small numerical trend favouring vemurafenib + cobimetinib for PFS, and a small numerical trend favouring dabrafenib + trametinib for OS. The submission suggested this may be due to differences in patient population characteristics, in particular a greater proportion of patients with elevated LDH levels in coBRIM. However, the submission also claimed that the differences across the trials were minor and would not impact on the outcomes of the indirect comparison. While the sponsor will not have access to the dabrafenib + trametinib data required to address this issue, ie assessment of OS by LDH level, such an analysis will be required to attribute the observed results to the cited patient characteristics. The ESC noted that the OS results were still immature at the time of submission.
- The trial exchangeability issues (LDH levels, exclusion due to brain metastases) and the ability of monotherapy patients in the COMBI-V trial to cross-over to dabrafenib + trametinib therapy suggested there is a potential for bias in the analyses and consequently the results of the indirect comparisons should be interpreted with caution. This was not considered to be a major issue by the ESC.
- ESC also noted that the Pre-Sub-Committee Response (PSCR) demonstrated that the 95% confidence intervals were narrower, and the lower 95% confidence limits were more supportive, for this comparison of the combinations than were generated in the evidence for the comparison of dabrafenib and vemurafenib alone previously accepted by the PBAC as supporting a non-inferiority conclusion.

6.15 The differences in safety data across the trials make clear conclusions on comparative safety difficult given the potential biases associated with any statistical comparisons. However, there were some indications of inferior safety with vemurafenib + cobimetinib. While the submission acknowledged the differences in adverse events between the two combinations, its claim that the AE profile is manageable with no additional cost implications was not strongly supported.

6.16 The submission stated that, should immunotherapies become PBS listed for use in previously untreated *BRAF* V600 mutation positive patients, it is proposed that vemurafenib + cobimetinib be made available following progression on immunotherapy. The evidence provided in support of this request is limited and does not adequately address the use of vemurafenib + cobimetinib following progression on immunotherapy. The submission also did not consider a comparison versus PD-1 inhibitors such as pembrolizumab and nivolumab, which would be informative should

immunotherapies be recommended for use in previously untreated *BRAF* mutation positive patients. The ESC noted that the treatment algorithm for melanoma is still evolving.

- 6.17 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.18 The PBAC considered that the claim of non-inferior comparative safety was weakly supported by the data, and PBAC also concluded that the toxicity profiles were different. For example, the trend to increased frequency of diarrhoea with vemurafenib + cobimetinib was considered against the fact that uncontrolled pyrexia has emerged as an issue with dabrafenib + trametinib.

**Economic analysis**

- 6.19 The submission presented a cost-minimisation analysis based on the indirect comparison of vemurafenib + cobimetinib compared to dabrafenib + trametinib.
- 6.20 The equi-effective doses were estimated as: vemurafenib 960 mg twice daily + cobimetinib 60 mg once daily (Days 1–21 of each 28 cycle) and dabrafenib 150 mg twice daily + trametinib 2 mg once daily. The cost-minimisation approach was based on the published approved ex-manufacturer price (AEMP) and was derived from a calculation of the equivalent costs per day and reflected the different periods of supply per dispensing. Calculations are shown in Table 6.

**Table 6: Cost-minimisation of vemurafenib + cobimetinib compared to dabrafenib + trametinib**

Name	Dose	AEMP	Supply period	Cost per day
Vemurafenib	960 mg, twice daily	\$ [REDACTED]	28 days	\$ [REDACTED] (= \$ [REDACTED] ÷ 28)
Cobimetinib	60 mg, once daily	\$ [REDACTED]	28 days	
<b>Total costs</b>		\$ [REDACTED]		
Dabrafenib	150 mg, twice daily	\$8,612.17	30 days	\$574.14 (= \$17,224.34 ÷ 30)
Trametinib	2 mg, once daily	\$8,612.17	30 days	
<b>Total costs</b>		\$17,224.34		

Source: adapted from Excel file “Cost-minimisation analysis”, worksheet “Summary of Costs” accompanying the submission. AEMP=approved ex-manufacturer price

The submission was lodged on the basis of price parity, in principle, for the combination therapies.

- 6.21 No concomitant medication costs were analysed. The validity of this analysis depends upon acceptance of the assumption that there are no differences in costs arising from very different AE profiles. This assumption was poorly supported. The PBAC noted that it was hard to compare AEs across trials and that there was no accounting for AE in the costing model.

**Drug cost/patient/28-day treatment cycle: \$ [REDACTED].**

- 6.22 Based on a median duration of treatment in coBRIM of [REDACTED] months, the estimated treatment cost per patient is would be \$ [REDACTED], while the cost for treatment over a full year would be \$ [REDACTED] (= \$ [REDACTED] × 365.25).

**Estimated PBS usage & financial implications**

- 6.23 This submission was not considered by DUSC, although the October 2015 DUSC report on the use of dabrafenib and ipilimumab was relevant to Section E of the submission. The submission used a market share approach based upon PBS online data collected for induction therapy with monotherapy dabrafenib.
- 6.24 The submission indicated that the requested listing was expected to have no financial impact as the combination treatments are cost-minimised to one another. The submission acknowledged that Special Pricing Arrangements apply to dabrafenib + trametinib, but the submission was lodged on the basis of price parity, in principle, for the combination therapies (ie the effective price of the individual components may vary, but the effective combination prices will be aligned).
- 6.25 Table 7 provides a summary of the estimated use of vemurafenib + cobimetinib and the estimated net cost to the PBS/RPBS, based on the published price of dabrafenib + trametinib.

**Table 7: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Eligible patients					
Market share	%	%	%	%	%
Number treated (vem + cob)					
Scripts <sup>a</sup>					
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Current market dabra + tram	\$	\$	\$	\$	\$
Future market dabra + tram	\$	\$	\$	\$	\$
Future market vem + cob	\$	\$	\$	\$	\$
Total future market	\$	\$	\$	\$	\$
<b>Net cost to PBS/RPBS</b>	<b>-\$</b>	<b>-\$</b>	<b>-\$</b>	<b>-\$</b>	<b>-\$</b>

Source: Table E.2.3, p4, Table E.4.1, p10 Section E-MS of the submission and 'Financial Cost to PBS' Excel file.

<sup>a</sup> Assuming scripts required per year per patient will be as estimated by the submission from the clinical trials (approx. ■ scripts).

cobi=cobimetinib; dabra=dabrafenib; tram=trametinib; vem=vemurafenib

The redacted table above shows that at year 5, the estimated number of scripts would be less than 10,000 and the net saving to PBS would be less than \$10 million.

- 6.26 Although no financial impact was predicted by the submission, the financial estimates indicated a net saving of less than \$10 million per year in the first year of listing, increasing to over less than \$10 million per year in year 5. Utilising effective prices decreased the estimated net savings, reflecting only the difference in script numbers due to different pack sizes (28 days for vemurafenib + cobimetinib versus 30 days for dabrafenib + trametinib).
- 6.27 The submission's estimates were not likely to be accurate, for the following reasons:
  - The submission did not include the use of ipilimumab in the determination of market size. Consequently, the market may be underestimated. In addition, the forecast market share for vemurafenib + cobimetinib (■% in year 1 increasing to a maximum of ■%) may also be an underestimate.

- Given the marked differences between the two combination treatments in their adverse event profiles, the assumption of equivalent cost of managing those events maintained by the submission, and exclusion of those costs from the financial estimates, may not be reasonable. While the impact of including such costs may not be large, the absence of AE costs means the submission's estimates are not likely to accurately reflect total cost to the PBS.
- ESC noted that the PSCR (p, 3) included a simple analysis which suggested that inclusion of AE would result in a ~ \$700 cost savings per individual, based on applying a single cost to serious AE generally (which slightly favours vemurafenib + cobimetinib).

6.28 The PBAC noted the proposed nil financial impact.

### ***Financial Management – Risk Sharing Arrangements***

6.29 The submission acknowledged that Special Pricing Arrangements apply to dabrafenib + trametinib and stated that the submission was lodged on the basis of price parity, in principle, for the combination therapies (ie the effective price of the individual components may vary, but the effective combination prices will be aligned). The submission also acknowledged that the sponsor would be required to share the existing Risk Share Arrangement caps under the Deed of Agreement previously agreed to by the sponsor of dabrafenib + trametinib.

6.30 The submission requested the PBAC make a 'pragmatic decision' to recommend a listing that allows for vemurafenib + cobimetinib to be prescribed either first or second line. This flexibility, it argued, would be appropriate in the event that immunotherapies are recommended by the PBAC for previously untreated *BRAF* mutation positive patients. The submission provided limited evidence to support the use of vemurafenib + cobimetinib following failure of immunotherapy, and did not provide any comparative evidence against PD-1 inhibitors, which would be alternate treatments should immunotherapies be recommended for use in previously untreated *BRAF* mutation positive patients. This proposal was rejected by the PBAC due to the lack of any supporting data.

6.31 The ESC advised that the PBAC consider the consequences of listing a subsequent medicine (cobimetinib) on a cost-minimisation basis to a current medicine (trametinib) while the MES for the current medicine remains incomplete. It was noted that the expected evidence base for trametinib is to be generated from overseas data rather than Australian data, so the proposed listing of cobimetinib would not contaminate the evidence generated for the trametinib MES. The PBAC considered that the listing of cobimetinib in combination with vemurafenib would not generate any concerns for the trametinib MES. However, the PBAC advised that any price consequence for the sponsor of trametinib following the conclusion of the trametinib MES would need to apply to the sponsor of cobimetinib, and also any rebate consequence for the sponsor of cobimetinib, if cobimetinib is listed before the pricing consequences for the sponsor of trametinib are finalised.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

### **Quality Use of Medicines**

- 6.32 The PBAC recommend that the use of QUM measures, including education of clinicians of possible AE associated with the use of vemurafenib in combination with cobimetinib should be undertaken by the sponsor to minimise possible harm to patients.

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of vemurafenib in combination with cobimetinib, for the treatment of *BRAF* V600 mutation positive unresectable or metastatic melanoma, on a cost-minimisation basis against dabrafenib + trametinib at an equi-effective dose of vemurafenib 960 mg twice daily + cobimetinib 60 mg once daily (Days 1–21 of each 28 cycle) versus dabrafenib 150 mg twice daily + trametinib 2 mg once daily.
- 7.2 The proposal to use vemurafenib + cobimetinib in *BRAF* mutation positive patients, following failure of immunotherapy was rejected by the PBAC on the basis that the sponsor failed to provide sufficient evidence of clinical benefit following failure of immunotherapy.
- 7.3 The PBAC considered that the combined use of dabrafenib + trametinib was the appropriate comparator for the combined use of vemurafenib + cobimetinib.
- 7.4 The PBAC accepted the clinical non-inferiority of vemurafenib + cobimetinib versus dabrafenib and trametinib based on the results of the indirect comparison, and noting the narrower 95% CIs in the current indirect comparison for both PFS and OS than for the previous acceptance of non-inferiority of vemurafenib versus dabrafenib.
- 7.5 The PBAC accepted the comparative safety non-inferiority of vemurafenib + cobimetinib versus dabrafenib + trametinib overall despite the different safety profiles reported, including the fact that uncontrolled pyrexia has emerged as an issue with dabrafenib + trametinib.
- 7.6 The PBAC was concerned that the economic modelling did not include any costs due to managing the different AE profile of vemurafenib + cobimetinib compared to dabrafenib + trametinib, however the committee did not consider this grounds to reject the listing of vemurafenib + cobimetinib on a cost-minimisation basis.
- 7.7 The PBAC noted that the sponsor of vemurafenib + cobimetinib would be required to share the current Risk Share Arrangement (RSA) with the sponsor of dabrafenib + trametinib, to ensure no additional cost to Government beyond current financial caps; and also any applicable price and rebate consequences following the conclusion of the trametinib MES to be applied to the price of cobimetinib.
- 7.8 Advice to the Minister under section 101 (3BA) of the Act  
The PBAC advised the Minister that there are no drugs or medicinal preparations that should be treated as interchangeable with vemurafenib + cobimetinib on an individual patient basis.

- 7.9 The PBAC advised that the combination of vemurafenib + cobimetinib is not suitable for prescribing by nurse practitioners.
- 7.10 The PBAC recommended that the Early Supply Rule should not apply.
- 7.11 The PBAC noted that this submission is not eligible for an Independent Review as it was a positive recommendation.
- 7.12 The PBAC noted that any V600 mutation would constitute a *BRAF* mutation for the purposes of determining eligibility for PBS-subsidised vemurafenib. No particular issue was identified that might be relevant to MSAC deliberations.

**Outcome:**

Recommended

**8 Recommended listing**

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer		
VEMURAFENIB 240 mg tablet, 56	4	3	ZELBORAF	Roche Products Limited	Pty

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<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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<b>Clinical criteria:</b>	<p>The condition must be positive for a <i>BRAF</i> V600 mutation,</p> <p>AND</p> <p>Patient must be receiving PBS subsidised cobimetinib concomitantly for this condition,</p> <p>AND</p> <p>The condition must not have been treated previously with PBS subsidised therapy, OR Patient must have developed intolerance to another combination BRAF/MEK inhibitor of a severity necessitating permanent treatment withdrawal,</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less.</p>
<b>Administrative Advice</b>	<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	№.of Rpts	Proprietary Name and Manufacturer	
VEMURAFENIB 240 mg tablet, 56	4	5	ZELBORAF	Roche Products Pty Limited

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	<p>Patient must have previously been issued with an authority prescription for this drug,</p> <p>AND</p> <p>Patient must have stable or responding disease.</p>

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<b>Administrative Advice</b>	<p>A patient who has had progressive disease when treated with this drug is no longer eligible for 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>
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Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
COBIMETINIB 20 mg tablet, 63	1	3	COTELLIC Roche Products Pty Limited

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	<p>Patient must be receiving PBS subsidised vemurafenib concomitantly for this condition,</p> <p>AND</p> <p>Patient must not have had progressive disease when treated with a BRAF inhibitor.</p>
<b>Administrative Advice</b>	<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	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
COBIMETINIB 20 mg tablet, 63	1	5	\$ [REDACTED]	COTELLIC Roche Products Pty Limited

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives

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<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	<p>Patient must have previously been issued with an authority prescription for this drug,</p> <p>AND</p> <p>Patient must be receiving PBS-subsidised vemurafenib concomitantly for this condition,</p> <p>AND</p> <p>Patient must have stable or responding disease.</p>
<b>Administrative Advice</b>	<p>A patient who has had progressive disease when treated with this drug is no longer eligible for 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>

**8 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.

**9 Sponsor's Comment**

The sponsor had no comment.