

7.7 TRAMETINIB
500 microgram tablet, 30,
2 mg tablet, 30;
Mekinist[®]; GlaxoSmithKline Australia Pty Ltd.

1 Purpose of Application

- 1.1 The resubmission includes a Managed Entry Scheme (MES) proposal to support its request for an Authority Required listing for trametinib, used in combination with dabrafenib, for treatment of patients with BRAF V600 mutation positive unresectable stage III or metastatic (stage IV) melanoma.

2 Requested listing

- 2.1 Suggested 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 (Packs)	No. of Rpts	Proprietary Name and Manufacturer	
TRAMETINIB			Mekinist	GK
500 microgram tablet, 30	3	3		
2 mg tablet, 30	1	3		

Category / Program	GENERAL – General Schedule (Code GE)
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
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	<i>Malignant melanoma</i>
PBS Indication:	Unresectable Stage III or Stage IV <i>malignant melanoma</i>
Treatment phase:	Initial
Restriction:	Authority required
Clinical criteria:	Must be used in combination with PBS-subsidised dabrafenib. <i>Patient must be receiving a PBS-subsidised BRAF V600 inhibitor concomitantly for this condition,</i> AND <i>Patient must not have progressive disease when treated with a BRAF inhibitor.</i>

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Administrative Advice	<p>A patient who has progressive disease when treated with a BRAF inhibitor is not eligible to receive PBS subsidised treatment with trametinib and dabrafenib.</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 (Packs)	No. of Rpts	Proprietary Name and Manufacturer	
TRAMETINIB			Mekinist	GK
500 microgram tablet, 30	3	5		
2 mg tablet, 30	1	5		

Category / Program	GENERAL – General Schedule (Code GE)
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
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	<i>Malignant melanoma</i>
PBS Indication:	Unresectable Stage III or Stage IV <i>malignant melanoma</i>
Treatment phase:	Continuing
Restriction:	Authority required
Clinical criteria:	<p>Must be used in combination with PBS subsidised dabrafenib.</p> <p><i>Patient must be receiving a PBS-subsidised BRAF V600 inhibitor concomitantly for this condition,</i></p> <p>AND</p> <p><i>Patient must have previously been issued with an authority prescription for this drug,</i></p> <p>AND</p> <p><i>Patient must not have progressive disease.</i></p>

<p>Administrative Advice</p>	<p>A patient who has progressive disease with a combination of trametinib and dabrafenib is no longer eligible for PBS subsidised treatment with trametinib and dabrafenib.</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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- 2.2 The basis of the MES proposal was a two-step evaluation process with the initial step (Evaluation 1) based on a cost-utility analysis comparing the efficacy and safety of trametinib in combination with dabrafenib with that of dabrafenib monotherapy as informed by the phase II BRF113220 trial. The second step (Evaluation 2) would be a future economic model based on completed phase III data.
- 2.3 In August 2014, the sponsor provided an update to the MES proposal, which consisted of headline results from the COMBI-V trial comparing trametinib plus dabrafenib combination therapy to vemurafenib monotherapy. The update used the COMBI-V results to provide support for the use of the BRF113220 trial in the modelled evaluation, but did not alter the structure or inputs of the original MES proposal.

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

3 Background

- 3.1 Trametinib was TGA registered on 14 February 2014 for the following indications:
- in combination with dabrafenib for the treatment of patients with BRAFV600 mutation positive unresectable stage III or metastatic (stage IV) melanoma
 - as a monotherapy for the treatment of patients with BRAFV600 mutation positive unresectable stage III or metastatic (stage IV) melanoma and in whom either there is intolerance to BRAF inhibitors or BRAF inhibitors cannot be used.

Trametinib as monotherapy was noted not to have demonstrated clinical activity in patients who have progressed on BRAF inhibitor therapy.

- 3.2 Trametinib was previously considered by the PBAC in March 2014. The submission was rejected on the basis that the superior comparative effectiveness of trametinib with dabrafenib over dabrafenib monotherapy had not been established (paragraph 7.1, March 2014 PBAC Minutes). The PBAC also considered that, in view of its concerns about the reliability of the BRF113220 trial, the ICER was not reliable (paragraph 7.3, March 2014 PBAC Minutes).
- 3.3 In regard to the sponsor's proposal to discuss a MES, the PBAC considered that, in view of the uncertain magnitude of the survival benefit indicated by current data, establishing an entry price that would be supported by the data and acceptable to the sponsor was problematic (paragraph 7.4, March 2014 PBAC Minutes).

4 PBAC concerns with the March 2014 submission

4.1 The key PBAC concerns were that the available evidence (BRF113220 and headline COMBI-D results) did not provide a robust basis for making a subsidisation recommendation and the ICER was not reliable given concerns about the reliability of the BRF113220 trial (paragraphs 7.2 and 7.3, March 2014 PBAC Minutes). In regard to the establishment of a managed entry scheme, the PBAC noted that in view of the uncertain magnitude of the survival benefit demonstrated by the available evidence, establishing an entry price that would be supported by the data and acceptable to the sponsor was problematic (paragraph 7.4, March 2014 PBAC Minutes). These concerns, along with additional concerns identified by the PBAC, and the MES proposal's response to the concerns, are listed in the summary table below.

Summary of PBAC concerns (March 2014)

PBAC concern	MES proposal response
Key concerns	
<ul style="list-style-type: none"> •The available evidence (BRF113220 and headline COMBI-D results) did not provide a robust basis for making a subsidisation recommendation and the ICER was not reliable given concerns with the reliability of the BRF113220 trial (paragraphs 7.2 and 7.3, March 2014 PBAC Minutes). •In regard to establishment of a managed entry scheme, the PBAC noted that in view of the uncertain magnitude of the survival benefit demonstrated by the available evidence, establishing an entry price that would be supported by the data and acceptable to the sponsor was problematic (paragraph 7.4, March 2014 PBAC Minutes). 	<ul style="list-style-type: none"> •The MES proposal maintains use of the same trial evidence as the March 2014 submission, and updates the economic model by decreasing the trametinib requested price and using progression-free survival (PFS) sensitivity analysis values from BRF113220 for the model base case. Consequently, the requested entry price is informed by trial evidence considered by the PBAC to be not robust and an economic model identified by the PBAC as not providing a reliable ICER.
Additional concerns	
<ul style="list-style-type: none"> •The place of trametinib in clinical practice, in particular use as monotherapy (paragraph 4.3, March 2014 PBAC Minutes). 	<ul style="list-style-type: none"> •The MES proposal states (p8) the sponsor does not believe there is an established patient population for the monotherapy indication.
<ul style="list-style-type: none"> •The trial exclusion criteria and patient demographics presented a challenge in interpreting trial results (paragraphs 6.5 and 6.7, March 2014 PBAC Minutes). 	<ul style="list-style-type: none"> •The MES proposal does not address this concern.
<ul style="list-style-type: none"> •COMBI-D data is preliminary (paragraph 6.10, March 2014 PBAC Minutes). 	<ul style="list-style-type: none"> •The MES proposal uses COMBI-D data to substantiate the use of BRF113220 BICR-based sensitivity analysis data. • The MES proposal also uses COMBI-V data to support the PFS and OS claims.
<ul style="list-style-type: none"> •Comparative safety may be worse than the 'moderately inferior' profile claimed by the submission (paragraph 6.25, March 2014 PBAC Minutes). 	<ul style="list-style-type: none"> •The MES proposal argues that the rates of AEs were not underestimated in the previous submission. This argument fails to acknowledge that the trial design may have underestimated AEs given the exclusion criteria (i.e., patients at risk of cardiac and ocular events were excluded). •The MES proposal changes the clinical claim for safety, stating that trametinib combined with dabrafenib is associated with a different, but no worse tolerability profile than dabrafenib monotherapy.
<ul style="list-style-type: none"> •The differences in health state definitions in the 	<ul style="list-style-type: none"> •The MES proposal does not address this concern.

PBAC concern	MES proposal response
model potentially over-estimated the utility gain from avoiding progressive disease (paragraph 6.27, March 2014 PBAC Minutes).	
•The utility values were overestimated for clinical response and underestimated for decrement due to AEs (paragraph 6.35, March 2014 PBAC Minutes).	•The MES proposal does not address the issue of overestimation of utilities for clinical response and argues that AE disutility was appropriately specified.
•The full cost of treating the higher rate of AEs associated with combination therapy were not appropriately captured in the submission (paragraph 6.38, March 2014 PBAC Minutes).	•The MES proposal does not address this concern.
•Use of trametinib would increase time on treatment and therefore utilisation and cost of dabrafenib (paragraph 6.39, March 2014 PBAC Minutes).	•The MES proposal increases estimated treatment duration with both trametinib and dabrafenib in its updated Section E estimates.

AEs=adverse events; BICR=blinded independent central review; MES=managed entry scheme
Source: Compiled during the evaluation

5 Proposed MES

5.1 The MES proposal sets out two evaluation points, as follows:

- Evaluation 1: 2014, based on current phase II economic model, the decision criterion to set the trametinib price is a base case ICER range of \$45,000/QALY - \$75,000/QALY (as determined by previously accepted oncology examples, such as dabrafenib where there is significant clinical need and some uncertainty in OS advantage). No further modelling was conducted to incorporate the early COMBI-D data.
- Evaluation 2: (timing uncertain as event driven) when COMBI-D and COMBI-V survival data are final, based on future phase III economic model. The decision criterion to set the trametinib price is a base case ICER range of \$75,000/QALY - \$105,000/QALY (as determined by previously accepted oncology examples where there is significant clinical need and OS advantage is proven).

5.2 Under Evaluation 1, the proposed entry price of \$ [REDACTED] results in an ICER of \$45,000/QALY - \$75,000/QALY, which falls into the range specified by the proposal. The MES proposal states (p16) that the proposed price is contingent on agreement to a special pricing arrangement. The Pre-Sub-Committee Response (PSCR) (p4) stated that a special pricing arrangement would be managed through a Deed of Agreement for trametinib where the published price is rebated to ensure the cost to Government is the same as the proposed entry price.

5.3 The model used is the same as that presented in the March 2014 submission (Markov model with 3 health states and a 5-year duration) except the hazard ratio (HR) value for PFS used in the model has been changed to that based on the blinded independent central review (BICR) sensitivity analysis from BRF113220, and the requested price of trametinib (\$ [REDACTED]) has been decreased [REDACTED]% from that requested in the March 2014 submission (\$ [REDACTED]). Model results, including the March 2014 ICER, are provided in the table below.

Results of the updated economic model (decreased trametinib price; PFS using BRF113220 sensitivity analysis values)

Component (no steps)	Combination	Monotherapy	Increment
Costs			
QALY			
Incremental cost/extra QALY gained			
Incremental cost/extra QALY gained March 2014			

Source: Excel model 'Section D Workbook.xls' accompanying the March 2014 submission and Table 3, of the MES proposal.

- 5.4 In addition to the issues raised regarding non-conservative utility weights and extrapolation models, PFS and OS were extrapolated independently in the economic model. The ESC considered that a multi-way sensitivity analysis to assess the impact on OS from changing PFS could be informative. The ESC also advised that the basis for fitting the modelled survival curves against the observed data should be examined in sensitivity analysis. The pre-PBAC response stated that the modelled survival curve used had been selected mainly because it resulted in the most conservative estimate of incremental survival.
- 5.5 The MES proposal argued that the BICR-based sensitivity analysis, which has a PFS of median 9.2 months for combination therapy and 7.3 months for dabrafenib monotherapy (HR=0.54; 95% CI: 0.32, 0.91), is appropriate to use as the PFS values are similar to the PFS values observed in sensitivity analyses of the COMBI-D trial. The MES proposal provided no statistical assessment of the similarity of PFS values between the trials. Use of the BICR-based sensitivity analysis PFS value in the updated model has little impact on the ICER. The key driver of the decrease in ICER from the March 2014 value is the drop in requested price for trametinib.
- 5.6 The PBAC considered that the ICER produced by the March 2014 model was not reliable, given the Committee's concerns with the reliability of the BRF113220 trial (paragraph 7.3, March 2014 PBAC Minutes). In addition, the PBAC indicated the model was likely to overestimate utility values for clinical response and underestimate disutility values (paragraph 6.35, March 2014 PBAC Minutes). The ESC agreed that the MES proposal does not alter the updated model to address these concerns. It is likely that details of the proposed future economic model as well as details of an exit scheme would minimise the uncertainty with the current MES proposal.
- 5.7 The ESC recalled that the PBAC had previously considered that the BRF113220 trial did not provide a robust basis for making a subsidisation recommendation (paragraph 7.2, March 2014 PBAC Minutes), however the economic model only uses data from this study. The ESC noted that the COMBI-V trial offered the most complete data set, but it was not possible to validate the economic model using these trial data because the model structure does not allow for data from the other trials to be inputted.
- 5.8 The PSCR (p4) stated that the sponsor is considering its approach to the proposed future model and is investigating whether it is feasible and appropriate to estimate PFS and OS by pooling the patient level data from the three trials. The ESC considered that, although COMBI-D and COMBI-V are similar in design, adjustment might be needed as the COMBI-V trial was halted prematurely and trials stopped

early tend to overestimate the size of effect. An assessment of whether pooling introduces significant imbalance across key patient-level characteristics would be necessary once data are sufficiently mature to pool. If and where imbalance exists, the statistical contingencies required to adjust for any such between-trial heterogeneity would need to be determined.

- 5.9 Evaluation 2 assumed that the PBAC would apply a higher ICER/QALY range (ICER of \$75,000/QALY - \$105,000/QALY) without identifying any precedent for PBAC to adopt this range. In the absence of any clear precedent, the basis for valuing confidence differently across the two evaluations is inadequately justified. The PBAC rejected this proposal for a higher ICER/QALY range for Evaluation 2, noting that the suggested premise (that the later data would prove an OS advantage) had already been accepted; the residual uncertainty now relates to estimating the magnitude of clinical benefit.
- 5.10 The ESC noted that the sponsor did not provide a managed exit scheme proposal that would address the circumstances where the observed treatment effect in the future or new data arising from the COMBI-D trial is smaller than anticipated. The ESC considered that it may be appropriate to have an arrangement such as a Deed of Agreement defining how to address this risk, should the cost-effectiveness of trametinib not be supported by future data and modelling.
- 5.11 The PBAC considered that a MES, modified from that proposed in the resubmission, would be appropriate to address the uncertainty related to the magnitude of clinical benefit while providing early access to those patients for whom there is a high clinical need. The PBAC noted that its current reconsideration was based on the updated results modelled from the BRF113220 trial, estimating incremental life years gained (LYG) of ■■■■, incremental QALYs gained of ■■■■, and an ICER of \$45,000/QALY - \$75,000/QALY. If the modelled survival holds true in the future, then the proposed ICER (of Evaluation 1) is deemed to be of acceptable cost effectiveness. The PBAC considered that any MES for trametinib should be guided by the following conditions.
- The initial price for the MES would be as requested from Evaluation 1, with the ICER of \$45,000/QALY - \$75,000/QALY based on modelling from the BRF113220 trial. This is despite unresolved concerns that the ICER still favours trametinib. Instead of recommending trametinib at a price justified by the existing evidence (which would be lower), a rebate with interest would be put in place, thereby ensuring that the conditions of the MES framework are fulfilled. On submission of modelling based on more conclusive evidence of cost-effectiveness from COMBI-D and COMBI-V (Evaluation 2), there would be no option for an increase in the price of trametinib, as the higher price is being paid at entry into the PBS. The PBAC noted that there would be no justification for applying a higher ICER following evaluation of COMBI-D/V (Evaluation 2) since the ICER of \$45,000/QALY - \$75,000/QALY is already high, as are the total budgetary implications.
 - The possible outcomes following Evaluation 2 of the MES would be that either:
 - the price of trametinib (or dabrafenib) would reduce; or
 - the price of trametinib would be maintained.
 - The arrangement proposed places the financial burden on the Commonwealth for the upfront risk associated with the uncertain clinical benefit of trametinib. Accordingly, should the extent of benefit of trametinib modelled from trial

BRF113220 fail to be realised in the final COMBI-D and COMBI-V results, then the sponsor would rebate the Commonwealth taking account of the following:

- the price reduction of trametinib would be calculated to maintain the current ICER (\$45,000/QALY - \$75,000/QALY) with reduced clinical benefits
- the rebate would be calculated by multiplying this price reduction by the number of PBS-dispensed prescriptions of the combination between the date of listing and the date of implementation of the price reduction (relating to either dabrafenib or trametinib), after applying
- an interest rate deemed appropriate by the Commonwealth. The repayment would apply to dabrafenib + trametinib.
- Evaluation 2 should include an individual patient data (IPD) based meta-analysis using final results of both arms from all three trials. If this approach was determined to be methodologically difficult, then the final COMBI-D trial results should be used (since this study has the greatest applicability to the anticipated use of trametinib in clinical practice in Australia, i.e. with dabrafenib). The BRF113220 trial results could also be withdrawn from the meta-analysis if the sponsor is concerned about cross-over in this trial “contaminating” the meta-analysis, noting that the small sample size of this trial means that it would have low weight in the requested meta-analysis.
- Evaluation 2 should be provided as soon as possible (and expected to be within two years) after maximal follow-up of the COMBI-D trial, noting that the final analysis of OS for COMBI-D is expected to report in late April 2015.
- The clinical evaluation for Evaluation 2 should formally report the meta-analyses for both PFS and OS using the standard graphics of Kaplan-Meier curves, and with standard reporting of results (log rank p-values, hazard ratios with 95% confidence intervals, medians, difference in medians, etc.).
- The economic evaluation for Evaluation 2 should use direct meta-analysis IPD curves to estimate incremental PFS and incremental OS up to the median duration of follow-up across the two arms compared in the clinical evaluation, and then allow extrapolation modelling on both arms for both PFS and OS curves from this timepoint, i.e. no statistical adjustments for crossover.
- The PBAC considered the other inputs to the model need not change for the economic evaluation in Evaluation 2, despite the fact that the associated biases are in favour of trametinib. These include (a) utilities for the progression-free health state and the post-progression health state, (b) the costs of additional adverse effects and (c) not adjusting for the trial populations excluding patients with brain metastases whilst including these patients in the requested PBS population.

5.12 The PBAC noted that these modifications to the resubmission’s proposal also represent modifications to the MES framework which was prepared in the context of the 2010-2014 Memorandum of Understanding between the Commonwealth and Medicines Australia.

- Although the PBAC is expected under this existing framework to recommend coverage at a price justified by the existing evidence, and the PBAC view is that the existing evidence would require a reduced price, this expectation is essentially fulfilled with these modifications by putting in place a rebate plus interest.
- Although submission of more conclusive evidence of cost-effectiveness is expected under this existing framework to support listing of the medicine at a

higher price, there should be no option for a higher price with these modifications because a higher entry price is being offered for initial listing.

- Consistent with this existing framework, the MES arrangements for trametinib would need to be formalised in any Deed of Agreement established for the purposes of PBS listing.
- Consistent with this existing framework, the nature of these arrangements (without details of the consequences for pricing) should be made public, particularly to inform other sponsors of these modifications.
- Consistent with this existing framework, any other unexpected but relevant developments emerging before Evaluation 2, such as unexpected safety signals, would be considered according to usual PBAC processes.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The PBAC considered that the hearing was not informative as it did not add substantively to the evidence presented in the resubmission.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item, but recalled it had received 3 comments in March 2014.

Clinical trials

- 6.3 The update to the MES proposal received in August 2014 contained headline results from the COMBI-V trial. To allow consideration of evidence presented across all documents provided by the applicant since the March 2014 submission, a summary of all trials is provided here.
- 6.4 Details of the trials presented in the resubmission (BRF113220), the PSCR (COMBI-D) and the update to the MES proposal (COMBI-V) are provided in the table below.

Trials and associated reports presented in the resubmission, PSCR and update to the MES proposal

Trial ID	Protocol title/ Publication title	Publication citation
BRF113220	An open-label, dose-escalation, phase IB/II study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of the BRAF Inhibitor GSK2118436 in combination with the MEK Inhibitor GSK1120212 in subjects with BRAF mutant metastatic melanoma (Part C). Flaherty KT, Infante JR, Daud A et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations	2013 NEJM, 367(18), 1694-1703.
COMBI-D	A Phase III, randomized, 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.	2014

COMBI-V	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	2014
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6.5 The key features of the randomised trials are summarised in the table below.

Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Primary outcome	Use in modelled evaluation
Trametinib 2mg/day combined with dabrafenib 150mg/bd vs. dabrafenib 150mg/bd						
BRF113220 (Part C)	162 ^a	R, OL, MC On-going (Phase II)	Low ^b	First line unresectable stage III) or metastatic (stage IV) melanoma	PFS, OS	Parametric survival functions fitted to PFS and OS extrapolated to 5 years
COMBI-D	423	R, DB, MC On-going (Phase III)	Low		PFS	None
Trametinib 2mg/day combined with dabrafenib 150mg/bd vs. vemurafenib 960mg/bd						
COMBI-V	704	R, OL, MC Trial halted (Phase III)	Low	First line unresectable stage III) or metastatic (stage IV) melanoma	OS	None

^a Includes 54 patients randomised to trametinib 1mg in combination with dabrafenib 150mg/bd (regimen not directly relevant to the evaluation of treatment effect).

^b While the risk of systematic error in BRF113220 is low, the fact that the trial was powered to assess a reduction in cutaneous squamous cell carcinoma as an adverse event and was not powered to assess treatment effect through PFS or OS raises concerns about potential sources of error.

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

Source: compiled during the evaluation

6.6 Results provided in the update to the MES proposal for COMBI-V are included in the summary below.

Results from BRF113220, COMBI-D and COMBI-V

		COMBI-V	COMBI-D	BRF113220		
Overall survival						
Data cut-off		17 Apr 2014	26 Aug 2013	31 May 2012	29 Mar 2013	15 Jan 2014
Combination 150/2 (n/N % alive)		252/352 (72%)	171/211 (81%)	40/54 (74%)	28/54 (52%)	
Monotherapy (n/N % alive)		230/352 (65%)	157/212 (74%)	35/54 (65%)	23/54 (43%)	
Absolute difference		7%	7%	9%	9%	
Median months (95% CI)	Combination 150/2	NR (18.3, NR)	NR (14.1, NR)	NR	23.8 (17.5, NR)	
	Monotherapy	17.2 (16.4, NR)	NR	NR (13.4, NR)	20.2 (14.5, 25.9)	
	Absol diff	-	-	-	3.6	
Relative difference HR (95% CI)		0.69 (0.53, 0.89)	0.63 (0.42, 0.94)	0.67 (0.34, 1.34)	0.73 (0.43, 1.24)	
Progression free survival						
Data cut-off		17 Apr 2014	26 Aug 2013	31 May 2012	29 Mar 2013	15 Jan 2014

Combination 150/2 (n/N % no progression)		186/352 (53%)	109/211 (52%)	23/54 (43%)	Not reported
Monotherapy (n/N % no progression)		135/352 (38%)	103/212 (49%)	7/54 (13%)	
Absolute difference		15%	3%	30%	
Median months (95% CI)	Combination 150/2	11.4 (9.9, 14.9)	9.3 (7.7, 11.1)	9.4 (8.6, 16.7)	
	Monotherapy	7.3 (5.8, 7.8)	8.8 (5.9, 10.9)	5.8 (4.6, 7.4)	
	Absol diff	4.1	0.5	3.6	
Relative difference HR (95% CI)		0.56 (0.46, 0.69)	0.75 (0.57, 0.99)	0.39 (0.25, 0.62)	

Absol diff=absolute difference; NR=not reached

Source: Table 1, p2 and Table 3, p3 of the PSCR; ESMO presentation provided with the PSCR; Table 25, p76 of the March 2014 submission; Table 1, p13 of the MES proposal; Table 3, p5 and Table 4, p6 of the update to the MES proposal

- 6.7 The update to the MES proposal notes that the COMBI-V trial has been halted due to a statistically and clinically significant overall survival benefit in favour of the trametinib and dabrafenib combination arm.
- 6.8 The update to the MES proposal claims that the COMBI-V results provide support for the accuracy of the BRF113220 results upon which the economic model was based. This claim is centred on the update's claim that the OS hazard ratios are similar across the trials, thereby providing support for the use of BRF113220 data in the model. While the hazard ratio point estimates for OS are similar across the trials, the 95% CIs differ considerably and demonstrate differences in trial results, with BRF113220 showing a non-significant difference for OS. The update also claims that COMBI-V results support the argument made by the sponsor that adverse event (AE) rates are not underestimated in BRF113220. This claim does not address the fact that the rate observed in the trial may be an underestimate given that BRF113220 excluded patients who were at risk of cardiovascular and ocular AEs.
- 6.9 The ESC considered that the COMBI-V data provided the PBAC with more confidence that trametinib + dabrafenib significantly increases the OS gain over a BRAF inhibitor alone. The PBAC considered that further analysis from COMBI-D would be useful, despite acknowledging that the new data from COMBI-V did address the uncertainty the PBAC had with regard to whether there was an effect on OS in its previous consideration. This contributes to why the PBAC considered that a MES was still needed.
- 6.10 The PBAC agreed with the ESC that a modelled evaluation based on data from both COMBI-V and COMBI-D would be informative, given that the BRF113220 trial has pre-existing issues regarding the reliability of its results.

Benefits/harms

- 6.11 A summary of the comparative harms for trametinib combination therapy versus dabrafenib monotherapy is presented in the table below. COMBI-V results are included. The values in the table below do not adjust for treatment exposure.
- 6.12 The MES proposal argues that the AE event rate was not underestimated in the March 2014 submission, as AEs were taken directly from the clinical study report.

The update to the proposal maintains this argument. However, this argument by the proposal fails to acknowledge that the trial design may have underestimated AEs given the exclusion criteria (i.e., patients at risk of cardiac and ocular events were excluded).

- 6.13 The MES proposal also states that ocular and cardiac toxicities occur at very low rates and given that patients have the life threatening illness of advanced melanoma these toxicities are not of clinical concern and can be managed with dose reductions or cessation of treatment in rare cases. The BRF113220 trial excluded patients at risk of cardiac and ocular events, therefore low rates of these events are not unexpected.

Summary of benefits and harms

Trial	Combination 150/2 therapy	Monotherapy	HR (95% CI)	Event-free rate/100 patients		Absolute difference
				Combination 150/2 therapy	Monotherapy	
Benefits						
Progression free survival^a						
COMBI-V 14 April 2014 cut-off	186/352	135/352	0.56 (0.46, 0.69)	53	38	15
COMBI-D 26 August 2013 cut-off	109/211	103/212	0.75 (0.57, 0.99)	52	49	3
BRF113220 31 May 2012 cut-off ^b	23/54	7/54	0.39 (0.25, 0.62)	43	13	30
Overall survival^c						
COMBI-V 14 April 2014 cut-off ^f	252/352	230/352	0.69 (0.53, 0.89)	72	65	7
COMBI-D 26 August 2013 cut-off ^d	171/211	157/212	0.63 (0.42, 0.94)	81	74	7
BRF113220 31 May 2012 cut-off ^b	40/54	35/54	0.67 (0.34, 1.34)	74	65	9
BRF113220 29 March 2013 cut-off ^e	28/54	23/54	0.73 (0.43, 1.24)	52	43	9
BRF113220 15 Jan 2014 cut-off	■	■	■	■	■	■

	Combination 150/2 therapy	Monotherapy	RR (95% CI)	n/N (%)		RD (95% CI)
				Combination 150/2 therapy	Monotherapy	
Harms						
Any drug related SAE						
COMBI-V						
COMBI-D						
BRF113220	16/55	10/53	1.54 (0.79, 3.08)	29.1	18.9	0.10 (-0.06, 0.26)
Pyrexia						
COMBI-V						
COMBI-D						
BRF113220	8/55	1/53	7.71 (1.32, 46.78)	14.5	1.9	0.13 (0.03, 0.25)
Chills						
COMBI-V						
COMBI-D						
BRF113220	6/55	1/53	5.78 (0.96, 36.02)	10.9	1.9	0.09 (-0.004, 0.20)

^a No progression or death.

^b median 14 months follow-up.

^c Proportion alive.

^d median 9 months follow-up.

^e median 24 months follow-up.

^f median 21 months follow-up (Kaplan-Meier curve; Figure 1, p6 of the update to the MES proposal)

SAE=serious adverse event

Source: compiled during the evaluation

- 6.14 On the basis of the COMBI-V data, for every 100 patients treated with trametinib and dabrafenib combination therapy, compared with vemurafenib alone:
- 7 more patients will be alive following a median 21 months follow-up;
 - 15 more patients will have not have progressed;
 - 2 more patients will have a drug-related serious adverse event;
 - 12 more patients will have pyrexia;
 - 4 more patients will have chills.
- 6.15 On the basis of the COMBI-D data, for every 100 patients treated with trametinib and dabrafenib combination therapy, compared with dabrafenib alone:
- 7 more patients will be alive following a median 9 months follow-up;
 - 3 more patients will have not have progressed. Given immaturity of the data, the median follow-up is unknown;
 - 5 more patients will have a drug-related serious adverse event;
 - 8 more patients will have pyrexia;
 - 3 more patients will have chills.

- 6.16 On the basis of the BRF113220 data, for every 100 patients treated with trametinib and dabrafenib combination therapy, compared with dabrafenib alone:
- Approximately 9 more patients will be alive following a median 14 months follow-up;
 - Approximately 9 more patients will be alive following a median 24 months follow-up;
 - Approximately 30 more patients will have not have progressed following a median 14 months follow-up;
 - Approximately 10 more patients will have a drug-related serious adverse event;
 - Approximately 13 more patients will have pyrexia;
 - Approximately 9 more patients will have chills.

Clinical claim

- 6.17 The update to the MES proposal assumed that trametinib combined with dabrafenib has a significant clinical benefit compared to dabrafenib monotherapy and is associated with an acceptable tolerability profile. In regard to safety, this differs slightly from the claim in the original MES proposal that indicated combination therapy had a different, but no worse tolerability profile than dabrafenib monotherapy. The claims made in the MES proposal and its update both differ from the March 2014 submission, where it was claimed that combination therapy was moderately inferior to dabrafenib monotherapy in regard to safety.
- 6.18 The PBAC considered that the claim of superior comparative effectiveness of trametinib with dabrafenib over dabrafenib monotherapy was reasonable, but noted that the magnitude of the treatment effect was still uncertain.
- 6.19 The PBAC considered that the revised claim of different, but no worse comparative safety of trametinib with dabrafenib to dabrafenib monotherapy was reasonable, noting a decrease in rate of cutaneous hyperproliferative events and photosensitivity, but increase in rate of pyrexia and ejection fraction decrease. The PBAC revisited its consideration of comparative safety given the new data provided from the COMBI-V trial.

Drug cost/patient/month: \$ [REDACTED].

- 6.20 The cost per patient per month assumes [REDACTED] pack of trametinib per month (treatment covers [REDACTED] of a month). Section E of the resubmission estimates assume patients would be treated for [REDACTED], which is rounded up to [REDACTED] to determine cost per course of therapy. The cost per course of therapy is \$ [REDACTED] assuming [REDACTED] of treatment.

Updated estimated PBS usage & financial implications

- 6.21 This MES proposal was not considered by DUSC. The proposal maintains the approach used in the March 2014 submission but with the use of BICR-based PFS data the mean duration of treatment, and therefore script numbers, increases for both combination therapy and dabrafenib monotherapy. The table below provides updated financial estimates.

Updated estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	█	█	█	█	█
Scripts ^a	█	█	█	█	█
Scripts ^a March 2014	█	█	█	█	█
Estimated net cost to PBS/RPBS/MBS/State governments					
Net cost to PBS/RPBS	█	█	█	█	█
Net cost PBS/RPBS March 2014	█	█	█	█	█
Net cost MBS	█	█	█	█	█
Net cost MBS March 2014	█	█	█	█	█
Net cost state/territory gov't	█	█	█	█	█
Estimated total net cost					
Net cost to government	█	█	█	█	█
Net cost to government March 2014	█	█	█	█	█

^a Combined number of scripts for trametinib and dabrafenib

Source: Excel workbooks supplied with the MES proposal and the March 2014 submission.

The redacted table above shows that at Year 5, the estimated number of patients treated is less than 10,000 and the net cost to Government is \$20 - \$30 million.

- 6.22 With the assumed longer treatment duration, the numbers of scripts have increased by less than 10,000 per year compared to the March 2014 estimates. Overall net costs have decreased by approximately \$10 - \$20 million per year given the drop in requested price, with an estimated total net cost over the first 5 years of listing of \$█. Given that the assumed treatment duration is informed by a trial that the PBAC considered to be not reliable (paragraphs 6.8 and 7.2, March 2014 PBAC Minutes), the estimates provided are not likely to be accurate.

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

7 PBAC Outcome

- 7.1 The PBAC recommended an Authority required listing of trametinib, for use in combination with dabrafenib, for the treatment of patients with BRAF V600 mutation positive unresectable stage III or metastatic (stage IV) malignant melanoma.
- 7.2 The PBAC recalled that, in March 2014, it had rejected the submission for trametinib on the basis that superior comparative effectiveness of trametinib with dabrafenib over dabrafenib monotherapy had not been established. In this current resubmission, the PBAC considered that new data provided from the COMBI-V trial provided the Committee with more confidence that trametinib with dabrafenib has an incremental

effect on overall survival (OS) over a BRAF inhibitor alone, and noting the clinical need and importance of early access to this patient population, recommended listing under a managed entry scheme (MES). The PBAC was satisfied that trametinib, when used in combination with dabrafenib, is more effective than dabrafenib alone, however the size of the incremental treatment effect is still uncertain, particularly for OS. This uncertainty is the basis for the MES.

- 7.3 Given the number of people with melanoma in Australia, the PBAC also considered it important that access to melanoma medicines was broadened and not confined only to those centres where clinical trials or special access arrangements are available. There remains a clinical need for early subsidised access because the duration of effect of BRAF inhibitors is short-lived, and this is expected to be extended to some extent when BRAF inhibitors are used in combination with MEK inhibitors.
- 7.4 In making its recommendation, the PBAC considered that data from the clinical trials presented is reassuring, however the extent of benefit modelled from the BRF113220 trial appears overestimated compared with the results to date from the larger COMBI-V and COMBI-D trials. The sponsor has provided reassurances that more robust evidence will be forthcoming in the foreseeable future to better inform its modelling, and the PBAC has proposed a plan to review this evidence within two years, to make sure patients receiving medicines on the PBS are being treated according to the best available evidence and that the cost of the combination therapy remains justified in terms of acceptable cost-effectiveness. Should the modelled extent of benefits not be realised, the Committee has recommended measures to minimise risk of unjustified health care expenditure.
- 7.5 The resubmission's nominated comparator of dabrafenib monotherapy (150 mg twice a day) remained unchanged from the comparator nominated in the March 2014 trametinib submission. The PBAC recalled that it had previously considered this to be appropriate in March 2014.
- 7.6 In March 2014, the trametinib submission was based on the Phase II BRF113220 trial and subsequently data emerging from the COMBI-D trial was provided. The update to the current resubmission included new data from the COMBI-V trial. The PBAC recalled that BRF113220 was not designed as an efficacy trial and was not considered to be a robust basis for making a subsidisation recommendation. The PBAC considered that the results from the two Phase III trials, COMBI-D and COMBI-V, would be more informative, noting that COMBI-D is ongoing and COMBI-V was halted prematurely due to a statistically and clinically significant overall survival benefit in favour of the trametinib and dabrafenib combination arm over the vemurafenib arm.
- 7.7 The PBAC considered that the claim of superior comparative effectiveness of trametinib with dabrafenib to dabrafenib monotherapy was reasonable, noting however the uncertainty with the extent of incremental effectiveness and duration of benefit.
- 7.8 The PBAC accepted that trametinib with dabrafenib had a different safety profile to dabrafenib monotherapy.

- 7.13 The PBAC noted that listing of trametinib would have flow-on restriction changes to dabrafenib, specifically removal of “The treatment must be the sole PBS-subsidised therapy for this condition” under the clinical criteria.
- 7.14 The PBAC recommended that trametinib should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.15 The PBAC advised that trametinib is not suitable for prescribing by nurse practitioners.
- 7.16 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.17 The PBAC noted that this resubmission is not eligible for an Independent Review.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	No. of Rpts	Proprietary Name and Manufacturer	
TRAMETINIB			Mekinist	GK
500 microgram tablet, 30	3	3		
2 mg tablet, 30	1	3		

Category / Program	GENERAL – General Schedule (Code GE)
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
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial
Restriction:	Authority required
Clinical criteria:	Patient must be receiving PBS-subsidised dabrafenib concomitantly for this condition, AND Patient must not have had progressive disease when treated with a BRAF inhibitor.

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Administrative Advice	<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 (Packs)	No. of Rpts	Proprietary Name and Manufacturer	
TRAMETINIB			Mekinist	GK
500 microgram tablet, 30	3	5		
2 mg tablet, 30	1	5		

Category / Program	GENERAL – General Schedule (Code GE)
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
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Continuing
Restriction:	Authority required
Clinical criteria:	<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 dabrafenib concomitantly for this condition,</p> <p>AND</p> <p>Patient must have stable or responding disease.</p>
Administrative Advice	<p>A patient who has 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>

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

GlaxoSmithKline welcomes the PBAC recommendation and will work with the Government to ensure listing of trametinib for the treatment of patients with V600 mutation positive unresectable Stage III or Stage IV malignant melanoma in a timely manner.