5.15 TRAMETINIB, 30, 0.5 mg tablet, 30 and 2 mg tablet, 30 Mekinist® GlaxoSmithKline Australia Pty Ltd.

1 Purpose of Application

1.1 The major submission sought an Authority Required General Schedule 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) melanoma

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
TRAMETINIB			Mekinist® GSK
Tablet 0.5mg	90	3	
Tablet 2mg	30	3	

Section 85 Authority required
Initial treatment, in combination with PBS-subsidised dabrafenib therapy, of patients with BRAF V600 mutation positive advanced (unresectable stage III) or metastatic melanoma, in a patient who has a WHO performance status of 2 or less.

Continuing treatment beyond 4 months of a patient with BRAF V600 mutation positive unresectable and/or metastatic melanoma, who has previously been issued with a prescription for trametinib who has stable or responding disease.
Notes:
A patient who has progressive disease when treated with a BRAF inhibitor is not eligible to receive PBS-subsidised treatment with trametinib and dabrafenib.
No applications for increased maximum quantities and/or repeats will be authorised.
Special Pricing Arrangements apply.

2.1 Trametinib is registered on the ARTG for strengths of 0.5 mg, 1 mg and 2 mg. The submission sought listing of the 0.5 mg and 2 mg strengths only.

2.2 The basis of the requested listing was a cost-utility analysis comparing the efficacy and safety of trametinib in combination with dabrafenib with that of dabrafenib monotherapy in the treatment of BRAF V600 mutation positive unresectable stage III or metastatic (stage IV) melanoma.

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 had not been previously considered by the PBAC.

4 Clinical place for the proposed therapy

4.1 Mitogen-activated extracellular signal regulated kinase (MEK) proteins are critical components of the extracellular signal-regulated kinase (ERK) pathway. In melanoma and other cancers, this pathway is often activated by mutations in BRAF, which activates MEK and stimulates tumour cell growth. Trametinib is a reversible, highly selective, allosteric inhibitor of MEK1 and MEK2. Trametinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.

4.2 The submission proposed the use of trametinib in combination with dabrafenib as first line treatment of patients with BRAFV600 mutation positive unresectable stage III or metastatic (stage IV) melanoma.

4.3 The PBAC considered that the place of trametinib in clinical practice requires clarification. Although trametinib monotherapy was not part of the submission (and was excluded by the proposed restriction), the PBAC noted that trametinib is registered for use in patients with intolerance to BRAF inhibitors or where BRAF inhibitors cannot be used. Also clinical guidelines (NCCN version 2014) support the use of monotherapy in these patient groups. For these reasons, it is important to estimate the percentage of patients who would be treated with monotherapy trametinib.

Given the increased toxicity of combination therapy and the possibility that primary resistance to monotherapy BRAF inhibitors may be anticipated (eg through molecular profiling) PBAC also requested clarification on whether all patients would commence on combination therapy or some patients would transition to combination therapy in the event of failure to respond or inadequate response to dabrafenib.

5 Comparator

5.1 The submission nominated dabrafenib monotherapy (150 mg twice a day) as the comparator. The PBAC considered this is was the appropriate comparator.

6 PBAC consideration of the evidence

Consumer comments and sponsor hearing

6.1 The PBAC noted the input from health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with trametinib including ability to return to work and suggestions on the use of trametinib. The PBAC noted the advice received from Medical Oncology Group of Australia Incorporated (MOGA) clarifying the likely use of trametinib in clinical practice.

6.2 The sponsor requested a hearing for this item. The sponsor presented clinical case studies and discussed the natural history of the disease, how the drug would be used in practice.

Clinical trials

6.3 The submission was based one head-to-head randomised trial comparing two alternative strengths of combination therapy of trametinib and dabrafenib to dabrafenib monotherapy, the BRF113220 trial. The BRF113220 trial comprised Parts A (Drug-Drug Interaction), B (Dose Escalation), C (Randomised Phase II) and D

(HPMC Capsules). Part C was presented as the pivotal evidence presented in the submission, shown below:

Trial	N	Design/ duration	Patient population	Outcome	Use in modelled evaluation
Trametinib 2mg combined with dabrafenib 150mg BID vs. dabrafenib 150mg BID					
BRF 113220 (Part C)	162[a]	OL, R, MC On-going (Phase II)	First line **unresectable stage III) or metastatic (stage IV) melanoma**	PFS, OS	Parametric survival functions fitted to PFS and OS extrapolated to 5 years

[a] Includes 54 patients randomised to trametinib 1mg in combination with dabrafenib 150mg BID daily (regimen not directly relevant to the evaluation of treatment effect).
MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised
Source: compiled during the evaluation.(ESC ADV .3)

6.4 The PBAC noted that BRF113220 was not designed as an efficacy trial. It was designed to investigate the safety, pharmacokinetics, pharmacodynamics, and clinical activity of dabrafenib in combination with trametinib. Recruitment was increased from 20 patients per arm to 50 by protocol amendment, to allow adequate power to show a reduction in the rate of cutaneous squamous cell carcinomas (cuSCC) from 20% with dabrafenib monotherapy to 3% for combination therapy. It was not designed to evaluate the effect on progression-free survival (PFS) and overall survival (OS). The PBAC noted the sponsor's claim in the PSCR that "…as BRF113220 was not designed to assess the efficacy endpoint of PFS, any claim… of (the trial) being underpowered for PFS and OS is methodologically inappropriate".

6.5 The PBAC noted that patients being treated for brain metastases were excluded from BRF113220. The PBAC considered that these patients are likely to comprise a significant proportion of the treatment population, having previously accepted that approximately 20% of patients with metastatic melanoma present with metastatic disease in the brain. Patients at risk of a range of cardiovascular conditions and ocular events were also excluded. The PBAC noted the sponsor's assertion in its PSCR that the exclusion criteria were established with regard to patient safety and were not expected to impact on the primary efficacy effect of combination dabrafenib and trametinib treatment. Overall, however, the PBAC considered that the trial exclusion criteria presented a challenge in interpreting the results of BRF113220.

6.6 The PBAC noted the baseline characteristics of the BRF113220 trial:

Summary of baseline characteristics

Baseline characteristics for patients enrolled to BRF113220 (Part C) (N=162[#])			
Baseline characteristics	**Monotherapy patients in BRF113220 (Part C) (N=54)**	**Combination 150/2 therapy patients in BRF113220 (Part C) (N=54)**	**Crossover patients in BRF113220 (Part C) (N=43)**
Male; female	54% male; 46% female	63% male; 37% female	49% male; 51% female
Mean age	51.8 years	55.9 years	50.8 years
WHO status	0=63%; 1=37%	0=65%; 1=35%	0=56%; 1 =42%; 2=2%
BRAFV600 mutation	V600E=83% V600K=17%	V600E=87% V600K=13%	V600E=84% V600K=16%
Staging:	Staging: Stage IV (98%) and IIIC (2%);	Staging: Stage IV (100%) and IIIC (0%);	Staging: Stage IV (98%) and IIIC (2%); 65% were M1c.

Baseline characteristics for patients enrolled to BRF113220 (Part C) (N=162[#])			
	69% were M1c	70% were M1c	
Disease sites:.	63% had ≥3 sites and 37% <3 sites.	52% had ≥3 sites and 48% <3 sites.	58% had ≥3 sites and 42% <3 sites.
No history of brain metastases:	93%	96%	93%

[#] Includes 54 patients randomised to sub-optimal dose of dabrafenib 150mg BID and trametinib 1mg QD. Listing is sought for combination 150/2 therapy.
Source: Adapted during evaluation from Table 12, p60 and Table 13,p.62 of the submission.

6.7 The PBAC noted that BRF113220 recruited predominantly patients with stage IV disease, while listing was sought for stage III and IV disease. The PBAC considered that this complicated the assessment of the effectiveness of trametinib with dabrafenib in stage III disease.

6.8 Overall, the PBAC did not consider the BRF113220 trial to be a robust basis for making a subsidisation recommendation.

6.9 The sponsor also presented the headline results, reported in January 2014, of a head-to-head trial (MEK115306 [COMBI-D] trial) in its Pre-Sub-Committee Response (PSCR). COMBI-D is a two-arm, double-blinded, randomised, Phase III study comparing combination 150/2 therapy to dabrafenib monotherapy plus placebo. It is being conducted in 121 sites including six in Australia. Subjects with histologically confirmed cutaneous melanoma that is either unresectable stage IIIC or stage IV, and BRAF V600E/K mutation positive have been recruited.

6.10 The PBAC noted that COMBI-D was considerably larger in size (N=423) and more balanced in regards to the disease stages than BRF113220. The PBAC considered that COMBI-D may provide a more reliable basis for assessing the comparative effectiveness of trametinib with dabrafenib, but noted the preliminary nature of the COMBI-D data.

Comparative effectiveness

6.11 The results from COMBI-D and BRF113220, are shown below:

	Combination 150/2 therapy n/N (PFS%)	***Monotherapy n/N (PFS%)***	***Absolute difference RD (95% CI)***	***Relative difference HR (95% CI)***
Progression free survival[a] – COMBI-D				
26 Aug 2013 cut-off	[redacted]	[redacted]	[redacted]	*0.75 (0.57, 0.99)*
Median months PFS (95% CI)	*9.3* [redacted]	*8.8* [redacted]	*0.5*	*-*
Overall survival[a] – COMBI-D				
26 Aug 2013 cut-off	*171/211 (81%)*	*157/212 (74%)*	*7%*	*0.63 (0.42, 0.94)*
Median months OS (95% CI)	*-* [redacted]	*-*	*-*	*-*
Progression free survival[a] – C				
31 May 2012 cut-off[b]	*23/54 (43%)*	*7/54 (13%)*	*30%*	*0.39 (0.25, 0.62)*
Median months PFS (95% CI)	*9.4 (8.6, 16.7)*	*5.8 (4.6, 7.4)*	*3.6*	*-*
Overall survival[c] – BRF113220 (Part C)				
31 May 2012 cut-off[b]	*40/54 (74%)*	*35/54 (65%)*	*9%*	*0.67 (0.34,1.34)*
29 March 2013 cut-off[d]	*28/54 (52%)*	*23/54 (43%)*	*9%*	*0.73 (0.43,1.24)*

[a] No progression or death for PFS; proportion alive for OS
[b] median 14 months follow-up.
[c] Proportion alive; censored with follow-up on-going.
[d] median 24 months follow-up.
OS=overall survival; PFS=progression-free survival
Source: Table 1, p2 and Table 3, p3 of the PSCR; Table 25, p76 of the submission.

6.12 The PBAC noted that based on the results of COMBI-D, the estimate of PFS benefit of trametinib plus dabrafenib over dabrafenib monotherapy was only 0.5 months. The PBAC noted that the median PFS gain estimated in BRF113220 was 3.6 months.

6.13 The PBAC noted that the PSCR presented the following sensitivity analyses of PFS for COMBI-D:

- Inclusion of symptomatic progressive disease as an event – median PFS [redacted] months for trametinib with dabrafenib vs. [redacted] months for dabrafenib monotherapy.
- Inclusion of the start of a new anti-cancer therapy as an event – [redacted] months vs. [redacted] months
- Ignoring extended loss to follow up and start of new anti-cancer therapy – [redacted] months vs. [redacted] months.

6.14 The PBAC noted that in the pre-PBAC response, the sponsor commented that in contrast to all the observed efficacy parameters in the combination arm of COMBI-D (which were consistent with those observed previously in BRF113220), the observed median PFS in the control dabrafenib monotherapy arm was markedly higher (8.8

months, CI: [redacted]) than observed in any previous trials (in which the median PFS ranged from 4.5 - 6.9 months). The PBAC noted that the sponsor is undertaking further analyses to understand the dabrafenib PFS monotherapy data in the COMBI-D trial, focusing in particular on early censoring in both arms of the COMBI-D trial.

6.15 The PBAC considered that the higher PFS for dabrafenib monotherapy in COMBI-D may be reflective of the greater experience of prescribers in managing AEs such as fever in clinical practice. Better management of AEs would plausibly reduce discontinuations and permit more sustained treatment with dabrafenib, potentially giving rise to a better-than-expected PFS result.

6.16 The PBAC noted from the sponsor's pre-PBAC response that similar median PFS values of 9.4 [95% CI: 8.6, 16.7] and 9.3 [95% CI: [redacted]] months were reported for combination treatment in both BRF113220 and COMBI-D, respectively. The sponsor claimed, with due caution regarding interpretation of cross-study comparisons, that the concordance of these two sets of results provides assurance that the clinical estimate of the effect size seen in BRF113220 is reliable despite the phase II nature of BRF113220.

6.17 Based on the extended data cut-off of 29 March 2013, the median OS in the dabrafenib monotherapy group was 20.2 months compared to 23.8 months in the combination 150/2 group. However, the PBAC noted that 83% of dabrafenib monotherapy patients crossed over to receive combination therapy. The PBAC also noted that the OS data were not mature, and the protocol specified threshold of 75% deaths had not been reached for final analysis, based on the data cut-off at 31 May 2012

6.18 The PBAC noted the similarity of the median PFS values from the two trials. However, the Committee considered that in view of the issues with the design of BRF113220 and the preliminary nature of the data from COMBI-D, it was not possible to conclude that either trial gave a reliable estimate of the clinical benefit of trametinib with dabrafenib combination therapy.

Comparative harms

6.19 The PBAC noted a greater occurrence of pyrexia ([redacted] vs. [redacted]), diarrhoea ([redacted] vs. [redacted]), chills ([redacted] vs. [redacted]) and vomiting ([redacted] vs. [redacted]) associated with combination therapy compared to dabrafenib monotherapy in COMBI-D.

6.20 A summary of the comparative harms for trametinib combination therapy versus dabrafenib monotherapy is presented in the table below. The values in the table below do not adjust for treatment exposure.

Table ES.3: Summary of harms

Trial	Combination 150/2 therapy	Monotherapy	HR (95% CI)	Event rate/100 patients		Absolute difference
				Combination 150/2 therapy	Monotherapy	
Benefits						
Progression Free Survival[a]						
COMBI-D 26 August 2013 cut-off	[redacted]	[redacted]	0.75 (0.57,0.99)	[redacted]	[redacted]	[redacted]
BRF113220 31 May 2012 cut-off[b]	23/54	7/54	0.39 (0.25,0.62)	43	13	30

Trial	Combination 150/2 therapy	Monotherapy	HR (95% CI)	Event rate/100 patients		Absolute difference
				Combination 150/2 therapy	Monotherapy	
Overall survival[c]						
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
	Combination 150/2 therapy	**Monotherapy**	**RR (95% CI)**	**n/N %**		**RD % (95% CI)**
				Combination 150/2 therapy	**Monotherapy**	
Harms						
Any drug related SAE						
COMBI-D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRF113220	16/55	10/53	1.5 (0.8, 3.1)	29.1	18.9	10.2 (-6.1, 26.2)
Pyrexia						
COMBI-D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRF113220	8/55	1/53	7.7 (1.3, 46.8)	14.5	1.9	12.7 (2.7, 24.6)
Chills						
COMBI-D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRF113220	6/55	1/53	5.8 (1.0, 36.0)	10.9	1.9	9.0 (-0.4, 20.3)

[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.
SAE=serious adverse event
Source: compiled during the evaluation

6.21 On the basis of the COMBI-D data, the PBAC noted that 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.

6.22 The PBAC also noted that these adverse events would be incurred from a treatment for which the magnitude of the clinical benefit was difficult to determine, but was possibly as small as a gain of 2 weeks in PFS.

Clinical claim

6.23 The submission claimed trametinib in combination with dabrafenib is superior to dabrafenib monotherapy with respect to comparative effectiveness and moderately inferior with respect to comparative safety.

6.24 The PBAC considered that in view of the immature survival data, the submission's estimate of the precise size of the treatment effect was not reliable. The PBAC therefore considered that the submission's claim of superior comparative effectiveness was not supported.

6.25 The PBAC noted the AEs associated with trametinib with dabrafenib combination therapy, and considered that the comparative safety may be worse than the "moderately inferior" profile claimed by the submission.

Economic analysis

6.26 The submission presented a cost-utility analysis. The results of the economic evaluation are shown in the table below:

Component (no steps)	Combination	Monotherapy	Increment
Costs	[redacted]	[redacted]	[redacted]
QALY	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			[redacted]

6.27 The PBAC noted that the clinical definitions of health states in the model were different to those used in Beusterien 2009, which are based upon WHO 1979 definitions. The protocol for BRF113220 (Part C) uses RECIST 1.1 criteria (Eisenhauer 2009)[1]. As a result, the economic model assigns the utility gain to some patients as if they achieve approximately ≥50% decrease in lesions (Beusterien et al 2009) when they have only achieved ≥30% decrease in lesions (BRF113220 [Part C]). The same applies to the definitions of progressive disease; ≥20% (BRF113220 [Part C]) increase in lesions compared to ≥25% increase in lesions (Beusterien et al 2009). Overall, the PBAC considered that the differences in definitions of health states potentially over-estimated the utility gain from avoiding progressive disease.

6.28 Furthermore, the submission adjusted disutility by duration of AE, assuming that disutility health states as measured in Beusterien 2009 last for one year. Minimal details on methods used to estimate utilities, including duration and framing of states valued in the standard gamble, were provided. Therefore, the PBAC considered that it was unclear whether the state described lasts for one year or less, or whether one year of treatment is described in which an AE happens for a certain period of time.

6.29 The transition probabilities used in the model were based on parametric survival functions (log-normal for PFS, gamma for OS) fitted to individual patient data from BRF113220 (Part C). The evaluation was not able to verify the model parameters given in the submission. The accuracy and precision of these estimates was therefore unknown, and only limited sensitivity analyses could be carried out given the constraints of the model.

6.30 The submission provided univariate sensitivity analyses only. The results ranged from $15,000-$45,000 (submission's upper estimate of OS), to monotherapy

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

dominating (lowest estimate of OS). Results were also sensitive to AE utility values. The PBAC agreed with the ESC that correct specification of disutilities was likely to result in an ICER over $100,000/QALY.

6.31 The PSCR, based on the COMBI-D trial, presented an ICER of $45,000-$75,000/QALY. According to the sponsor, "…preliminary and approximate estimation of the cost effectiveness of combination therapy using the COMBI-D results may be possible using an assumption of proportional hazards and application of the reported hazard ratios for PFS and OS to these outcomes for dabrafenib monotherapy generated from the BRF113220 study. It is recognised that this is inexact and rudimentary but has been applied to the model as a sensitivity analysis."

6.32 The PBAC noted that the model structure did not allow the values presented in the PSCR to be independently verified. The PBAC considered that the claims in the PSCR that "…the results indicate a reduced incremental cost and incremental outcome, however, the resulting ICER remains cost-effective,' could not be substantiated with the information provided.

6.33 The PBAC considered that the reliability of the base case ICER of the submission was affected by the lack of robustness in the clinical data, including trial design issues and lack of mature data. The PBAC noted the sensitivity of the ICER to PFS and OS, with a sensitivity analysis for OS resulting in dominance of monotherapy over combination therapy.

6.34 The submission used the rank preserving structural failure time model (RPSFTM) to adjust OS for the high crossover rate in the monotherapy arm. The submission did not justify the assumption of equal treatment effect in monotherapy patients (post crossover) and combination 150/2 therapy patients (post randomisation) that is required for RPSTFM.

6.35 The PBAC also considered that the utility values were overestimated for clinical response and underestimated for decrement due to AEs. The PBAC also considered that AEs were likely significantly underestimated in both rate of occurrence and average cost because the non-representative population excludes patients at risk of adverse events. The PBAC noted that the model is sensitive to the utility values.

Estimated PBS usage & financial implications

6.36 The submission was not considered by DUSC.

6.37 The table below presents the submission's estimated use and financial implications.

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated total net cost					
Net cost to Aust Govt.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Combined number of scripts for trametinib and dabrafenib as estimated by the submission.
Source: Table 124, p.241, Table 128, p.244, Table 131, p246 and Table 132,p.247 of the submission.

6.38 The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of $30 million to $60 million in Year 5.

6.39 The PBAC noted that the full costs of treating the higher rate of AEs associated with combination therapy were not appropriately captured in the submission.

6.40 The PBAC noted that the use of trametinib would increase the median time on treatment with, and therefore utilisation and cost of, dabrafenib. In the BRF113220 study, the duration of treatment on dabrafenib monotherapy was [redacted] months compared to [redacted] months for combination treatment.

6.41 The PBAC noted the sponsor's proposal of a managed entry scheme in its pre-PBAC response. The sponsor noted that two phase III trials are due to report in mid-2015, and estimated that a delay of approximately two years would be required to make a submission on the basis of mature Phase III survival data.

7 PBAC Outcome

7.1 The PBAC rejected the submission on the basis that the superior comparative effectiveness of trametinib with dabrafenib over dabrafenib monotherapy had not been established. The PBAC also noted the higher rate of AEs with combination therapy compared with dabrafenib monotherapy.

7.2 The PBAC considered that the BRF113220 trial did not provide a robust basis for making a subsidisation recommendation. The PBAC considered that the COMBI-D trial may inform future determinations of the treatment effect of trametinib, but noted that the current data are not mature.

7.3 The PBAC noted the sensitivity of the economic model to the estimates of survival and choice of utilities. The PBAC considered that, in view of it concerns with the reliability of the BRF113220 trial, the ICER was not reliable. The PBAC also noted that the model structure did not permit the estimates provided in the PSCR to be verified.

7.4 The PBAC noted the sponsor's proposal to discuss a Managed Entry Scheme for trametinib, noting that a delay of approximately two years could be incurred if it is necessary to wait until the OS data from the trials are mature. 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. Nonetheless, the PBAC considered it may be possible for a suitable proposal to be developed, and requested that the sponsor continue to liaise with the Department on this matter.

7.5 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

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.

Sponsor's Comment
GlaxoSmithKline is disappointed with the PBAC decision, but remains committed to working with the PBAC to make trametinib available on the PBS for patients with BRAF V600 mutation positive unresectable stage III or metastatic (stage IV) melanoma.