7.15 DABRAFENIB
Capsule 50 mg, 75 mg, Tafinlar®,
and
TRAMETINIB
Tablet 500 microgram, 2 mg, Mekinist®,
Novartis Australia Pty Ltd

1 Purpose of Application

1.1 The minor resubmission sought to address the outstanding areas of concern relating to the deferral of dabrafenib in combination with trametinib (dabrafenib+trametinib) as an adjuvant treatment for patients with BRAF V600 mutation positive resected Stage III melanoma at the March 2019 PBAC meeting.

1.2 This minor resubmission provided an updated proposed restriction, economic evaluation and financial implications, a revised pricing proposal, and a proposed risk-sharing arrangement (RSA) that covered the utilisation of dabrafenib+trametinib across the adjuvant and metastatic melanoma settings.

2 Background

2.1 Dabrafenib in combination with trametinib was registered by the TGA in June 2018 for the adjuvant treatment of patients with BRAF V600 mutation positive melanoma and involvement of the lymph node(s), following a complete resection.

2.2 Dabrafenib+trametinib was previously considered for this indication by the PBAC at its March 2019 meeting. At this meeting the PBAC deferred its decision. The PBAC acknowledged that there was a high unmet clinical need; however, considered that the results of the economic evaluation were unreliable and resulted in an uncertain cost-effectiveness ratio (paragraph 7.1, Dabrafenib+trametinib Public Summary Document (PSD), March 2019).

2.3 Table 1 provides a summary of the key issues identified by the PBAC at the March 2019 meeting and the manner in which the minor resubmission has addressed them.

Table 1: Key issues identified by the PBAC in March 2019 and how they were addressed in the minor resubmission

Issue identified by PBAC in March 2019 PSD	How issue was addressed in July 2019 resubmission
[paragraph 7.4] … the PBAC considered that patients may require more regular monitoring to determine any ongoing need for dose reduction. Therefore, the PBAC advised that 3 repeats would be more appropriate in the continuing phase (as per the initial phase). In addition, the PBAC considered that an Authority Required (telephone) would be appropriate for the initial supply to help reduce leakage into patients with Stage IIIA disease and the continuing supply to ensure treatment was capped at 12 months.	Addressed. The minor resubmission proposed 3 repeats for the initial and continuing phases. The minor resubmission proposed that the initial supply be supplied as an Authority Required (telephone). Not addressed. The continuing supply restriction was remained Authority Required (STREAMLINED).
[paragraph 7.12] The PBAC considered that the absolute RFS benefit and any potential OS benefit in the Stage IIIA subgroup to be particularly uncertain and likely to be modest, and not cost-effective at the same price as for Stages IIIB, IIIC and IIID. The benefit of adjuvant treatment in patients with Stage IIIA with metastases ≤ 1 mm was unknown as they were not represented in COMBI-AD. The PBAC considered that use of adjuvant dabrafenib+trametinib would be most beneficial and cost-effective in patients with Stage IIIB, IIIC and IIID disease.	Addressed. The requested restrictions were updated to restrict treatment to patients with Stage IIIB, IIIC and IIID disease.
[paragraph 7.15] The PBAC advised that the following re-specifications to the model structure and inputs would result in a more reliable ICER: • The modelled RFS and OS curves should converge from [redacted] to [redacted] years to reflect the uncertainty and immaturity of the data, in particular the modelled OS data were considered unreliable as it was based on events in 14% of patients in the dabrafenib+trametinib arm and 22% of patients in the placebo arm; • Treatment duration should be based on the mean duration of treatment observed in COMBI-AD (8.2 months for dabrafenib and 8.3 months for trametinib), rather than the modelled RFS (11.5 months); and • In order to account for wastage, treatment doses should be based on the TGA approved Product Information doses, rather than the average doses in the trial.	Addressed. Model structure and inputs were re-specified to: • Converge the RFS and OS curves from [redacted] to [redacted] years; • Use the mean duration of treatment observed in COMBI-AD (8.2 months for dabrafenib and 8.3 months for trametinib); and • Use treatment doses based on the TGA approved Product Information doses.
[paragraph 7.16] The PBAC noted that with convergence of the RFS and OS curves the ICER was sensitive to the utility values, and that the small utility gains assumed for avoiding recurrence were likely underestimated in the model. The PBAC considered that it may be reasonable for the respecified scenario to use utility values that better reflect the quality of life benefits of avoiding recurrence.	Not addressed. Utility values remained the same in the minor resubmission. This is conservative and results in the ICER being potentially overestimated.
[paragraph 7.17] The PBAC also noted that use of the published prices for pembrolizumab, nivolumab and ipilimumab as subsequent treatments for unresectable or metastatic disease increased the ICER, and advised that this would be taken into account when considering any revised proposal from the sponsor.	The minor resubmission applied a [redacted]% rebate to the published prices of pembrolizumab, nivolumab and ipilimumab.

Issue identified by PBAC in March 2019 PSD	How issue was addressed in July 2019 resubmission
[paragraph 7.18] The PBAC considered that the estimated number of patients likely to be treated with dabrafenib+trametinib were uncertain, and the following issues should be revised in a resubmission: • The use of outdated data (from 1959 to 2002, and based on the 6th edition of the AJCC staging system) to calculate the number of patients diagnosed with earlier stages of disease that would progress to Stage III disease; • a high assumed uptake rate of dabrafenib+trametinib in the adjuvant setting (%); • the inclusion of patients with Stage IIIA disease; and • the non-inclusion of grandfathered patients.	Addressed. Utilisation estimates were revised in the minor resubmission: • The minor resubmission used AIHW staging data, which resulted in a higher proportion of patients who progressed to Stage III disease from earlier stages (% versus % in the original submission); • Uptake was revised to % in Year 1 increasing to % in Year 6; • Patients with Stage IIIA were excluded. The Secretariat noted the submission's approach to exclude Stage IIIA patients was to lower the treatment uptake rates (p8 of the minor submission); and • Grandfathered patients ( ) were included in the Year 1 estimates.
[paragraph 7.19] The PBAC advised that the financial estimates should be updated to…..allow retreatment with dabrafenib±trametinib in the unresectable setting.	Partially addressed. The minor resubmission excluded cost offsets due to a reduction in use of subsequent therapies.
[paragraph 7.20] The PBAC considered that in the context of the uncertain use across the adjuvant and unresectable or metastatic settings, a RSA would be appropriate. The PBAC considered that any RSA should also include the current unresectable setting and include hard caps with 100% rebates.	Addressed. The minor resubmission proposed a RSA that covered utilisation in the adjuvant and unresectable or metastatic settings and proposed expenditure caps beyond which % rebates applied.

AIHW = Australian Institute of Health and Welfare; AJCC = American Joint Committee on Cancer; ICER = incremental cost-effectiveness ratio; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = Public Summary Document; RFS = recurrence free survival; RSA = Risk Sharing Arrangement; TGA = Therapeutic Goods Administration

For more detail on PBAC's view, see Section 5 PBAC outcome.

3 Requested listing

3.1 The resubmission requested the following updated PBS restrictions for both dabrafenib and trametinib in the initial, continuing and grandfather settings.

3.2 The proposed restrictions have been amended to align with the PBAC's suggestions following the March 2019 PBAC meeting. The number of repeats in the continuing phase were changed to three, treatment was restricted to patients with Stage IIIB, IIIC and IIID disease, and an Authority Required (telephone) restriction was requested for initial supply. The proposed restriction requested an Authority Required (STREMLINED) for continuing supply. This did not align with the PBAC's previous request for an Authority Required (telephone) for continuing supply to ensure that treatment was capped at 12 months. The PBAC reiterated an Authority Required (telephone) listing would be appropriate for continuing supply.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of repeats	DPMQ*	Proprietary Name and Manufacturer	
DABRAFENIB					
Capsule 50 mg, 120	1	Initial: 3 Continuing: 3	Published: $5,892.49 Effective: $[redacted]	Tafinlar®	Novartis Australia Pty Ltd
Capsule 75 mg, 120	1	Initial: 3 Continuing: 3	Published: $8,763.21 Effective: $[redacted]		
TRAMETINIB					
Tablet 500 microgram, 30	3	Initial: 3 Continuing: 3	Published: $6,610.14 Effective: $[redacted]	Mekinist®	Novartis Australia Pty Ltd
Tablet 2 mg, 30	1	Initial: 3 Continuing: 3	Published: $8,763.21 Effective: $[redacted]		

* Effective DPMQ prices are based on the weighted AEMPs (see Table 6)

Schedule:	General
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Category/program:	☒ Authority Required (telephone)
Severity:	Resected Stage IIIB, Stage IIIC or Stage IIID
Condition:	Malignant melanoma
Treatment phase:	Initial treatment
Clinical criteria:	The treatment must be adjuvant to complete surgical resection AND The condition must be positive for a BRAF V600 mutation AND Patient must have a WHO performance status of 1 or less AND Patient must be receiving PBS-subsidised trametinib and dabrafenib concomitantly for this condition AND ~~The condition~~ Patient must not have ~~been treated previously with~~ *received prior* PBS subsidised ~~therapy~~ *treatment for this condition.*
Treatment criteria:	Treatment must commence within 12 weeks of complete resection*, unless delay is necessary due to post-surgery recovery;* AND Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma ~~(initial and continuing therapy) under this restriction~~
Notes:	*No increase in the maximum quantity or number of units or number of repeats will be authorised. Special Pricing Arrangements apply.*

Schedule:	General
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Category/program	~~☒ Authority Required (STREAMLINED)~~ ☒ *Authority Required (telephone)*
Severity:	Resected Stage IIIB, Stage IIIC or Stage IIID
Condition:	Malignant melanoma
Treatment phase:	Continuing treatment
Clinical criteria:	Patient must have previously been issued with an authority prescription for trametinib and dabrafenib concomitantly for adjuvant treatment following complete surgical resection AND Patient must not have experienced disease recurrence
Treatment criteria:	Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma ~~(initial and continuing therapy) under this restriction~~
Notes:	*No increase in the maximum quantity or number of units or number of repeats will be authorised. Special Pricing Arrangements apply.*

Schedule:	General
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Category/program	~~☒ Authority Required (Streamlined)~~ ☒ *Authority Required (telephone)*
Severity:	Resected Stage IIIB, Stage IIIC or Stage IIID
Condition:	Malignant melanoma
Treatment phase:	Grandfather patients
Clinical criteria:	Patient must have previously received non-PBS subsidised drug for ~~this condition~~ *adjuvant treatment following complete surgical resection* prior to [list date] ~~AND~~ ~~The treatment must be adjuvant to complete surgical resection~~ AND The condition must be positive for a BRAF V600 mutation AND Patient must have a WHO performance status of 1 or less AND *The patient must not have evidence of recurrence* *AND* Patient must be receiving PBS-subsidised trametinib and dabrafenib concomitantly for this condition AND ~~The condition~~ Patient must not have ~~been treated previously with~~ *received prior* PBS subsidised ~~therapy~~ *treatment for this condition*
Treatment criteria:	Non-PBS subsidised treatment must have commenced within 12 weeks of complete surgical resection*, unless delay is necessary due to post-surgery recovery,* AND Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma ~~(initial and continuing therapy) under this restriction~~
Notes:	*No increase in the maximum quantity or number of units or number of repeats will be authorised. Special Pricing Arrangements apply.*

3.3 In March 2019 (paragraph 2.10, Dabrafenib+trametinib PSD) the PBAC considered that 'completely resected disease' would, in practice include all patients with a wide excision of the primary tumour and either complete lymph node biopsy (CLNB) or sentinel lymph node biopsy (SLNB) or both.

3.4 The PBAC previously considered that it would be 'clinically inappropriate to prevent retreatment if a patient had responded well to adjuvant therapy' (paragraph 7.3, Dabrafenib+trametinib PSD, March 2019). The resubmission therefore also provided updated amendments to the current restrictions for both dabrafenib and trametinib to allow retreatment in the metastatic setting.

3.5 Proposed additions to the current dabrafenib and trametinib listings are added in italics and proposed deletions are crossed out with strikethrough.

Dabrafenib	
Schedule:	General
Category/program:	Authority required (STREAMLINED)
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
Treatment phase:	Initial treatment
Clinical criteria:	The condition must be positive for a BRAF mutation, AND The ~~condition~~ *patient* must not have been treated previously with PBS subsidised therapy *for unresectable Stage III or Stage IV disease*; OR *The* patient must have developed intolerance to another BRAF inhibitor of a severity necessitating permanent withdrawal, AND Patient must have a WHO performance status of 2 or less
Treatment criteria:	Patients who have progressed during treatment with a BRAF inhibitor are no longer eligible to receive PBS-subsidised ~~dabrafenib~~ *treatment with this drug*

Trametinib	
Schedule:	General
Category/program:	Authority required (STREAMLINED)
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
Treatment phase:	Initial treatment
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.~~
Treatment criteria:	*Patients who have progressed during treatment with a BRAF inhibitor are no longer eligible to receive PBS-subsidised ~~trametinib~~ treatment with this drug*

3.6 The pre-PBAC response noted that changes to the current restrictions for the PD-1 inhibitors for the treatment of unresectable or metastatic melanoma would be required to limit first-line PD-1 use for BRAF V600 positive patients to those who had a recurrence during the 12 months of adjuvant dabrafenib + trametinib.

For more detail on PBAC's view, see Section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with adjuvant dabrafenib+trametinib for the treatment of completely resected Stage IIIB, IIIC and IIID melanoma including a reduced risk of recurrence, prolonged quality of life, the availability of an oral dosing form and few side effects.

4.3 The PBAC noted the correspondence received from Melanoma Patients Australia and the Australian Melanoma Consumer Alliance and the Melanoma Research Victoria Consumer Reference Group. These organisations reiterated their previous support for dabrafenib+trametinib, citing the high clinical need.

4.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for adjuvant dabrafenib+trametinib treatment for completely resected Stage IIIB, IIIC and IIID melanoma, categorising it as one of the therapies of 'highest priority for PBS listing' on the basis of the COMBI-AD Phase III trial. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for dabrafenib+trametinib, which was a Grade A. This is the highest grade (out of C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy of new potentially curative therapies), based on a comparison with placebo in the COMBI-AD trial.[1]

Clinical trials

4.5 As a minor resubmission, no new clinical evidence was presented.

Economic analysis

4.6 The pre-PBAC response to the March 2019 submission proposed an incremental cost-effectiveness ratio (ICER) of $15,000 - $45,000 per quality-adjusted life year (QALY).

4.7 To address the uncertainty identified by the PBAC in March 2019, the minor resubmission:

- re-specified the model structure and inputs to converge the recurrence free survival and overall survival curves from [redacted] to [redacted] years
- utilised the mean duration of treatment observed in COMBI-AD (8.2 months for dabrafenib and 8.3 months for trametinib), and
- used doses based on those recommended in the TGA approved Product Information to account for wastage.

4.8 In order to provide an ICER of less than $15,000 - $45,000 per QALY as requested by the PBAC, the minor resubmission also proposed a revised effective approved ex-

[1] Cherny N, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefits scale, version 1.1. *Annals of Oncology*. 2017; 28: 2340-2366.

manufacturer price (AEMP) for dabrafenib 75 mg, 120 and trametinib 2 mg, 30 of $[redacted] for adjuvant therapy. This was a [redacted]% reduction from that presented in the March 2019 submission and a [redacted]% reduction from that presented in the March 2019 pre-PBAC response.

4.9 The minor resubmission did not update the utility values as recommended by the PBAC to better reflect the quality of life benefits of avoiding recurrence (paragraph 7.16, Dabrafenib+trametinib PSD, March 2019). This favoured the observation arm of the model. The pre-PBAC response re-specified the model to include a 0.235 disutility for disease recurrence, which was calculated by taking the difference between the utilities for 'no treatment, 0.855' and 'recurrence, 0.62' from Middleton, 2017.

4.10 The revisions in the minor resubmission resulted in an ICER of $15,000 - $45,000 per QALY. Incorporation of the utility changes outlined in the pre-PBAC response resulted in an ICER of $15,000 - $45,000 per QALY.

Committee-In-Confidence information

4.11 The March 2019 model used the published prices for pembrolizumab, nivolumab and ipilimumab when considering subsequent treatment costs. The minor resubmission assumed a [redacted]% rebate on the published prices applied to these medicines. Using the prices the PBAC considered cost-effective for subsequent treatments resulted in an ICER of $[redacted] per QALY.

End Committee-in-Confidence information

Table 2: Results economic evaluation

	Dabrafenib+trametinib	Observation	Increment
July 2019 minor resubmission			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs gained	[redacted]	[redacted]	[redacted]
ICER per QALY gained			**$[redacted]**
Pre-PBAC response			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs gained	[redacted]	[redacted]	[redacted]
ICER per QALY gained			**$[redacted]**
March 2019 submission			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs gained	[redacted]	[redacted]	[redacted]
ICER per QALY gained			$[redacted]
ICER per QALY gained (pre-PBAC response)			$[redacted]

ICER = incremental cost-effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life-year
Source: Attachment 2 – Tafinlar (dabrafenib) and Mekinist (trametinib) Economic Evaluation – April 2019 – Excel spreadsheet and Table 16, p27 of the dabrafenib+trametinib PSD, March 2019 and p1-2 of the pre-PBAC response

The redated table shows an ICER of $15,000 – $45,000 per QALY.

Drug cost/patient/course: $[redacted]

4.12 The drug cost per patient was calculated from the economic model, which utilised the mean durations of treatment from the COMBI-AD trial (dabrafenib = 8.2 months;

trametinib = 8.3 months) and daily doses from the Product Information (dabrafenib = 300 mg per day; trametinib = 2 mg per day). The dispensed price for the maximum quantity (DPMQ) for both dabrafenib and trametinib was $[redacted] (AEMP = $[redacted]) for adjuvant therapy.

4.13 The drug cost per patient per 12 months treatment was calculated to be $[redacted].

Estimated PBS usage & financial implications

4.14 The following changes were made to the predicted use and financial implications of dabrafenib+trametinib:

- The minor resubmission used 2018 data from Cancer Australia that indicated 3% of melanoma patients had Stage III disease at diagnosis, rather than 8.4% from the Cancer Institute of NSW (2014), which was used in the March 2019 submission;
- The revised distribution of patients by stage using the Cancer Australia staging data (Stage I: 78%, Stage II: 14% and Stage III: 3%, compared to Stage I: 58%, Stage II: 26% and Stage III: 8.4% which were used in the March 2019 submission), resulted in a higher proportion of patients who progress to Stage III disease from earlier stages (approximately [redacted]%, compared with approximately [redacted]% from the March 2019 submission). This figure more closely aligned with the estimate from the Melanoma Institute Australia (55%);
- The Secretariat noted that uptake rates were reduced from [redacted]% in Years 1 to 6 of the March 2019 submission, to [redacted]% in Year 1, increasing to [redacted]% in Year 6 in lieu of the excluding of patients with Stage IIIA disease. The minor submission stated that Stage IIIA patients represented around 5% of Australian Stage III patients using the American Joint Committee on Cancer (AJCC) 8th edition, based on Haydu et al (2017);
- The addition of [redacted] grandfathered patients in Year 1;
- The exclusion of cost-offsets due to a reduction in use of subsequent therapies in the unresectable or metastatic setting. Patients with Stage III recurrent disease may develop recurrent unresectable disease that can include distant metastases. A reduction in subsequent therapies is expected due to reduced recurrence rates following treatment in the adjuvant setting. Further patients who have not tolerated dabrafenib+trametinib in the adjuvant setting will no longer receive this treatment in the unresectable or metastatic setting.

4.15 The following approaches used in the March 2019 submission were retained for the resubmission:

- Incident patients initially diagnosed with earlier stages of disease that progress to Stage III melanoma were included in the eligible population. The approach used the truncated (10-year) Kaplan-Meier curves of recurrence-free survival from the Sydney Melanoma Unit database for patients diagnosed with Stage I or II disease;

- The proportion of patients with resectable Stage III melanoma was assumed to be [redacted]% based on a market research survey which involved 31 medical oncologists; and
- The proportion of patients with BRAF V600 positive melanoma was calculated using a prevalence rate (44.5%) previously accepted by the MSAC when it considered the funding of BRAF mutation testing in patients with locally advanced or metastatic melanoma for eligibility for dabrafenib treatment (Application 1172 PSD, April 2013 MSAC meeting).

4.16 The updated utilisation and financial impact estimations are presented below. The Secretariat noted that the expected utilisation was significantly reduced ([redacted] and [redacted] patients in Year 1 and 6) compared to the March 2019 submission ([redacted] and [redacted] respectively) due to the use of the Cancer Australia incidence data and the reduction in treatment uptake rates. The net effective cost was reduced due to the reduction in utilisation and the reduced effective price presented in the March 2019 resubmission.

Table 3: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients						
Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate	[redacted]% ([redacted]%)[b]	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Total patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Units dispensed						
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trametinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total units dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the PBS and RPBS						
Net published cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net effective cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
March 2019 submission						
Total patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total units dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net effective cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
Source: Table 5-2, p9 of the minor resubmission and Table 19, p31 of the Dabrafenib+trametinib PSD, March 2019
a Grandfathered patients
b Proportion of grandfathered patients who meet the proposed PBS restriction

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year, and the net cost to the PBS would be $10 - $20 million per year.

Risk-sharing arrangement

4.17 The PBAC requested a RSA to account for the uncertain use across the adjuvant and unresectable or metastatic settings that included expenditure caps with 100% rebates (paragraph 7.20, Dabrafenib+trametinib PSD, March 2019).

4.18 To simplify the implementation of an RSA, the minor resubmission proposed a single weighted average effective AEMP for all strengths of dabrafenib and trametinib across the adjuvant and unresectable or metastatic settings.

4.19 The estimated utilisation of dabrafenib±trametinib in the unresectable or metastatic setting was based on a linear extrapolation of current use (August 2015 to July 2018) – see Table 4. The minor resubmission noted that there was a recent decline in the number of services processed for dabrafenib and trametinib, but considered that this would be temporary and was due to patients accessing immune oncology services through access programs and clinical trials. The actual utilisation for BRAF±MEK inhibitor therapy to 2018 is summarised below, based on the date of supply. The majority of use in 2018 (approximately 90%) was for dabrafenib+trametinib.

Table 4: Actual use of BRAF±MEK inhibitor therapy in the unresectable or metastatic setting

Unresectable or metastatic	2014	2015	2016	2017	2018
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prescriptions dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market growth	-	-	60%	11%	4%

Source: Department of Human Services Pharmacy Claims Database. Extracted on 17 June 2019 based on the date of supply

The redacted table shows less than 10,000 patients per year with 10,000 – 50,000 scripts dispensed in 2018.

4.20 The Secretariat, noting the declining growth in the number of prescriptions dispensed for BRAF±MEK inhibitor therapy, considered that the use of the linear extrapolation, which predicted approximately [redacted]% growth per year, overestimated use in future years (actual use in 2018 was 10,000 – 50,000 prescriptions, estimated use in 2019 was 10,000 – 50,000 prescriptions and in 2024 (i.e. Year 6) it was 10,000 – 50,000 prescriptions). The pre-PBAC response reiterated that the decline in use was likely due to increased use in clinical trials and access programs, and that these patients will need access to PBS subsidised medicines in the future.

4.21 The minor resubmission did not consider reduced use of dabrafenib±trametinib in the unresectable or metastatic setting due to:

- use of dabrafenib+trametinib in the adjuvant setting which resulted in a cure (the March 2019 submission assumed that this would result in approximately less than 10,000 less prescriptions dispensed in Year 6). The pre-PBAC response noted that the March 2019 estimate was based on higher utilisation due to the use of Cancer Australia utilisation data and higher assumed uptake rates. Using the updated data would result in a reduction of approximately [redacted] prescriptions in Year 6. The pre-PBAC response noted the impact of this on the relative use in the adjuvant versus unresectable or metastatic settings was marginal; and
- patients who have received dabrafenib+trametinib in the adjuvant setting receiving a PD-1 inhibitor (pembrolizumab or nivolumab) or CLTA-4 inhibitor (ipilimumab) rather than a BRAF± MEK inhibitor combination in the unresectable or metastatic setting. The pre-PBAC response noted that patients who receive 12

months of dabrafenib+trametinib as adjuvant treatment would be retreated with dabrafenib±trametinib in the unresectable setting.

Table 5: Total estimated dabrafenib and trametinib units dispensed

	Total estimated units dispensed – dabrafenib and trametinib					
	2019	2020	2021	2022	2023	2024
Adjuvant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unresectable or metastatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 5-2, p9 of the minor resubmission and Attachment 1 – Dabrafenib and trametinib utilisation and cost model – April 2019 – Excel

The redacted table shows 10,000 – 50,000 units dispensed in 2024.

4.22 The minor resubmission assumed utilisation in the adjuvant setting would be [redacted]%, with [redacted]% of use in the unresectable or metastatic setting.

Table 6: Weighted average effective AEMPs for dabrafenib and trametinib across the adjuvant and unresectable or metastatic settings

	Adjuvant ([redacted]%)	Metastatic ([redacted]%)	Weighted average AEMP
Dabrafenib 50 mg, 120	[redacted]	[redacted]	[redacted]
Dabrafenib 75 mg, 120	[redacted]	[redacted]	[redacted]
Trametinib 0.5 mg, 30	[redacted]	[redacted]	[redacted]
Trametinib 2 mg, 30	[redacted]	[redacted]	[redacted]

AEMP = approved ex-manufacturer price
Source: Table 2-1, p4 of the minor resubmission

4.23 The proposed expenditure caps, beyond which a [redacted]% rebate would apply, are presented below.

Table 7: Proposed expenditure caps (DPMQ – co-payment) for dabrafenib and trametinib

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Adjuvant use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unresectable/metastatic use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Expenditure caps	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DPMQ = dispensed price for maximum quantity
Source: Table 6-1, p9 of the minor resubmission

For more detail on PBAC's view, see Section 5 PBAC outcome.

5 PBAC Outcome

5.1 Following a deferral in March 2019, the PBAC recommended the listing of dabrafenib in combination with trametinib, on the PBS as a General Schedule listing, for the adjuvant treatment of patients with completely resected BRAF V600 mutation positive Stage IIIB, IIIC or IIID melanoma. The PBAC was satisfied that dabrafenib+trametinib provides, for some patients, a significant improvement in efficacy over routine follow-up, in terms of recurrence free survival, and a likely benefit in terms of overall survival, although there are currently limited data.

5.2 The PBAC acknowledged the consumer comments, which were again supportive of the PBS listing. In particular, the PBAC noted comments that there are no available

PBS-subsidised adjuvant treatment options for melanoma, that dabrafenib and trametinib are oral agents and that the adverse events are manageable.

5.3 The PBAC noted that the proposed restriction was amended to align with recommendations made in the March 2019 PSD, including restricting treatment to patients with Stage IIIB, IIIC or IIID disease, changing the number of repeats in the continuing stage to three and requesting an Authority Required (telephone) listing for initial supply. The PBAC noted that the submission requested an Authority Required (STREAMLINED) listing for continuing supply, and reiterated its advice from the March 2019 meeting that an Authority Required (telephone) would be appropriate for the continuing phase to ensure that treatment is capped at 12 months.

5.4 The PBAC noted the flow-on restriction changes to the current PBS listings for dabrafenib and trametinib (and the other BRAF±MEK inhibitors) to allow retreatment in the unresectable or metastatic setting for those patients who experience disease recurrence at least six months from completion of treatment in the adjuvant setting. The PBAC noted the flow-on restriction changes to the current PBS listings for the PD-1 inhibitors (nivolumab and pembrolizumab) for unresectable or metastatic disease to limit first-line PD-1 use for BRAF V600 positive patients to those who relapsed during adjuvant dabrafenib+trametinib treatment, or within six months from completion of adjuvant dabrafenib+trametinib treatment. The PBAC considered that similar flow-on restriction changes would be required for ipilimumab, when used in combination with nivolumab.

5.5 The PBAC noted that no new clinical evidence was provided in the minor resubmission.

5.6 The PBAC recalled that it had previously considered dabrafenib+trametinib superior compared to placebo in terms of recurrence free survival; however, due to the immaturity of the data, the magnitude of the treatment effect was uncertain. The PBAC recalled that it had previously considered dabrafenib+trametinib inferior compared to placebo in terms of comparative safety.

5.7 The PBAC noted that the economic model was re-specified as previously recommended so that the modelled recurrence free survival and overall survival curves converged from [redacted] to [redacted] years, treatment duration was based on the mean duration observed in COMBI-AD trial (8.2 months for dabrafenib and 8.3 months for trametinib) and doses were based on the TGA approved Product Information doses to account for wastage.

5.8 The PBAC noted the revised effective approved ex-manufacturer price (AEMP), and considered that the resulting incremental cost-effectiveness ratios (ICERs) (see paragraphs 4.10 and 4.11) were acceptable.

5.9 The PBAC considered that in the context of the uncertain use across the adjuvant and unresectable or metastatic settings, the proposal of a risk-sharing arrangement (RSA) consisting of subsidisation caps, across both adjuvant and unresectable or metastatic settings, beyond which [redacted]% rebates would apply was appropriate. The PBAC

considered that the use of a weighted average effective AEMP for all strengths of dabrafenib and trametinib across the adjuvant and unresectable or metastatic settings to be reasonable. The PBAC considered that should the effective price be weighted across the two populations, the weighting applied should be consistent with the agreed final financial estimates and joint RSA across the two settings.

5.10 The PBAC considered that the proposed expenditure caps for the adjuvant setting were appropriate. The PBAC noted that the current RSA subsidisation caps for BRAF±MEK inhibitors are significantly overestimated and are unlikely to represent the actual market for these medicines in the unresectable or metastatic setting. The PBAC therefore advised that the subsidisation caps for the unresectable or metastatic setting in the combined RSA should be based on the current actual PBS utilisation with a small reduction in utilisation as outlined in paragraph 4.20, due to patients receiving adjuvant treatment that resulted in a cure. The PBAC noted that it was estimated in the pre-PBAC response that there would be a reduction of approximately [redacted] prescriptions for the unresectable or metastatic setting by Year 6. The PBAC considered a reduction in use in the unresectable setting was unlikely to be observed in the first year of the adjuvant listing; however, from the second year onwards, a reduction in use in the unresectable or metastatic setting should be accounted for.

5.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for dabrafenib+trametinib:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over placebo in terms of recurrence free survival;
b) The treatment is expected to address a high and urgent unmet clinical need as there are currently no medicines for the adjuvant treatment of melanoma listed on the PBS; and
c) It would be in the public interest for the subsequent pricing application to be progresses under Pricing Pathway A on the basis of the preceding findings.

5.12 The PBAC recommended that dabrafenib+trametinib should not be treated as interchangeable on an individual patient basis with any other drugs.

5.13 The PBAC advised that the combination of dabrafenib+trametinib is not suitable for prescribing by nurse practitioners.

5.14 The PBAC recommended that the Early Supply Rule should not apply.

5.15 The PBAC noted that this submission is not eligible for an Independent Review as it was a positive recommendation.

Outcome:
Recommended

6 Recommended listing

6.1 Amend existing/recommended listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of repeats	Proprietary Name and Manufacturer	
DABRAFENIB				
Capsule 50 mg, 120	1	Initial: 3 Continuing: 3	Tafinlar	Novartis Australia Pty Ltd
Capsule 75 mg, 120	1	Initial: 3 Continuing: 3		
TRAMETINIB			Mekinist	Novartis Australia Pty Ltd
Tablet 500 microgram, 30	3	Initial: 3 Continuing: 3		
Tablet 2 mg, 30	1	Initial: 3 Continuing: 3		

Dabrafenib and trametinib	
Schedule:	General
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Category/program:	☒ Authority Required (telephone)
Severity:	Resected Stage IIIB, Stage IIIC or Stage IIID
Condition:	Malignant melanoma
Treatment phase:	Initial treatment
Clinical criteria:	The treatment must be adjuvant to complete surgical resection AND The condition must be positive for a BRAF V600 mutation AND Patient must have a WHO performance status of 1 or less AND Patient must be receiving PBS-subsidised trametinib and dabrafenib concomitantly for this condition AND Patient must not have received prior PBS-subsidised treatment for this condition.
Treatment criteria:	Treatment must commence within 12 weeks of complete resection, unless delay is necessary due to post-surgery recovery; AND Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma
Notes*:*	No increase in the maximum quantity or number of units or number of repeats will be authorised. Special Pricing Arrangements apply.

Dabrafenib and trametinib	
Schedule:	General

Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Category/program	☒ Authority Required (telephone)
Severity:	Resected Stage IIIB, Stage IIIC or Stage IIID
Condition:	Malignant melanoma
Treatment phase:	Continuing treatment
Clinical criteria:	Patient must have previously been issued with an authority prescription for trametinib and dabrafenib concomitantly for adjuvant treatment following complete surgical resection AND Patient must not have experienced disease recurrence
Treatment criteria:	Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma
Notes:	No increase in the maximum quantity or number of units or number of repeats will be authorised. Special Pricing Arrangements apply.

Dabrafenib and trametinib	
Schedule:	General
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Category/program	☒ Authority Required (telephone)
Severity:	Resected Stage IIIB, Stage IIIC or Stage IIID
Condition:	Malignant melanoma
Treatment phase:	Grandfather patients
Clinical criteria:	Patient must have previously received non-PBS subsidised drug for adjuvant treatment following complete surgical resection prior to [list date] AND The condition must be positive for a BRAF V600 mutation AND Patient must have a WHO performance status of 1 or less AND The patient must not have evidence of recurrence AND Patient must be receiving PBS-subsidised trametinib and dabrafenib concomitantly for this condition AND Patient must not have received prior PBS-subsidised treatment for this condition.
Treatment criteria:	Non-PBS subsidised treatment must have commenced within 12 weeks of complete surgical resection, unless delay is necessary due to post-surgery recovery, AND Treatment must not exceed a maximum duration of 12 months for adjuvant treatment of completely resected Stage IIIB, IIIC or IIID melanoma
Notes:	No increase in the maximum quantity or number of units or number of repeats will be authorised. Special Pricing Arrangements apply.

Flow-on changes to the current initial treatment restrictions for dabrafenib and trametinib (and vemurafenib+cobimetinib (currently PBS listed) and encorafenib+binimetinib (recommended in November 2018)) to allow retreatment in the unresectable or metastatic setting.

Dabrafenib (and vemurafenib and encorafenib)	
Schedule:	General
Category/program:	Authority required (STREAMLINED)
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
Treatment phase:	Initial treatment
Clinical criteria:	The condition must be positive for a BRAF mutation, AND The patient must not have been treated previously with PBS subsidised therapy for unresectable Stage III or Stage IV disease; OR The patient must have developed intolerance to another BRAF inhibitor of a severity necessitating permanent withdrawal, *AND* *If the patient has received dabrafenib plus trametinib in the adjuvant setting, the patient must not have experienced disease recurrence within 6 months of completion of adjuvant treatment* AND Patient must have a WHO performance status of 2 or less
Treatment criteria:	Patients who have progressed during treatment with a BRAF inhibitor are no longer eligible to receive PBS-subsidised treatment with this drug

Trametinib (and cobimetinib and binimetinib)	
Schedule:	General
Category/program:	Authority required (STREAMLINED)
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
Treatment phase:	Initial treatment
Clinical criteria:	Patient must be receiving PBS subsidised dabrafenib concomitantly for this condition
Treatment criteria:	Patients who have progressed during treatment with a BRAF inhibitor are no longer eligible to receive PBS-subsidised treatment with this drug

Flow on changes to the current initial treatment 1 restriction for the PD-1 inhibitors (nivolumab and pembrolizumab) in the unresectable or metastatic setting to limit first-line PD-1 use for BRAF V600 positive patients to those who relapsed during adjuvant dabrafenib + trametinib, or within six months of completion of adjuvant dabrafenib+trametinib. Flow on changes to ipilimumab, when used in combination with nivolumab, are yet to be finalised.

Nivolumab and pembrolizumab	
Category/Program:	Section 100 Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial treatment 1
Restriction level:	☒Streamlined

Clinical criteria:	The condition must be positive for a BRAF V600 mutation, AND The patient must have progressed following treatment with a BRAF inhibitor (with or without MEK inhibitor) *in the unresectable or metastatic setting* unless contraindicated or not tolerated according to the TGA approved Product Information, OR *The patient must have experienced disease recurrence whilst receiving dabrafenib plus trametinib as an adjuvant treatment for completely resected Stage IIIB, IIIC or IIID melanoma, OR* *The patient must have experienced disease recurrence within 6 months of completion of adjuvant dabrafenib plus trametinib treatment,* AND Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for ~~this condition~~ *the treatment of unresectable Stage III or Stage IV malignant melanoma,* AND The treatment must be the sole PBS-subsidised therapy for this condition, AND *Relevant dosage restriction for nivolumab and pembrolizumab.*

7 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.

8 Sponsor's Comment

Novartis welcomes the PBAC's decision to recommend dabrafenib+trametinib for adjuvant treatment of BRAF mutation positive melanoma patients.