PHARMAC
Pharmaceutical Management Agency

MEMORANDUM FOR BOARD MEETING 29 JULY 2016

To: PHARMAC Directors

From: Acting Chief Executive

Date: July 2016

Proposal for pembrolizumab, posaconazole and raltegravir

Recommendations

It is recommended that having regard to the decision making framework set out in Section 2.2 of PHARMAC's Operating Policies and Procedures you:

resolve to create a new Therapeutic Group (TG) 3 subheading "Programmed Cell Death 1 (PD 1) Inhibitors" under the Immunosuppressants TG2 subheading in the Oncology and Immunosuppressants therapeutic group in Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 September 2016;

resolve to move the current listing of nivolumab (Opdivo) from the "Monoclonal Antibodies" to the "Programmed Cell Death-1 (PD-1) Inhibitors" TG3 subheading in Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 September 2016;

resolve to list pembrolizumab (Keytruda) under the "Programmed Cell Death-1 (PD-1) Inhibitors" subheading in Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 September 2016 as follows (prices and subsidies expressed ex manufacturer, excluding GST):

Chemical	Brand	Presentation	Pack size	Price and subsidy
Pembrolizumab	Keytruda	Inj 50 mg vial	1	$2,340 00
Pembrolizumab	Baxter	Inj 1 mg for ECP	1 mg	$49.14

resolve to list pembrolizumab (Keytruda) in Section B of the Pharmaceutical Schedule subject to the following restrictions from 1 September 2016:

PCT only – Specialist

Special Authority for Subsidy
Initial Application — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1 Patient has metastatic or unresectable melanoma stage III or IV; and
2 Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and
3 Either:
  3.1 Patient has not received funded nivolumab; or
  3 2 Both:
    3.2.1 Patient has received an initial Special Authority approval for nivolumab and has discontinued nivolumab within 12 weeks of starting treatment due to intolerance; and

3.2.2 The cancer did not progress while the patient was on nivolumab; and

4 Pembrolizumab is to be used at a maximum dose of 2 mg/kg every 3 weeks for a maximum of 12 weeks (4 cycles); and

5 Baseline measurement of overall tumour burden is documented (see Note); and

6 Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of pembrolizumab will not be continued beyond 12 weeks (4 cycles) if their disease progresses during this time.

Renewal — (unresectable or metastatic melanoma) only from a medical oncologist**.** Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1 Any of the following:

1.1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or

1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or

1 3 Patient has stable disease according to RECIST criteria (see Note); and

2 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and

3 No evidence of progressive disease according to RECIST criteria (see Note); and

4 The treatment remains clinically appropriate and the patient is benefitting from the treatment; and

5 Pembrolizumab is to be used at a maximum dose of 2 mg/kg every 3 weeks for a maximum of 12 weeks (4 cycles).

Notes:
Disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1 1 (Eisenhauer EA, et al Eur J Cancer 2009;45:228-47) Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements. Target lesion measurements should be assessed using CT or MRI imaging with the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

- Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non target) must have reduction in short axis to <10 mm
- Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease

resolve to list pembrolizumab (Keytruda) in Part II of Section H of the Pharmaceutical Schedule subject to the following restrictions from 1 September 2016:

Restricted
Initiation
Medical oncologist
Re assessment required after 4 months
All of the following:

1 Patient has metastatic or unresectable melanoma stage III or IV; and

2 Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and

3 Either:

3 1 Patient has not received funded nivolumab; or

3.2 Both:

3 2 1 Patient has received an initial Special Authority approval for nivolumab and has discontinued nivolumab within 12 weeks of starting treatment due to intolerance; and

3.2.2 The cancer did not progress while the patient was on nivolumab; and

4 Pembrolizumab is to be used at a maximum dose of 2 mg/kg every 3 weeks for a maximum of 12 weeks (4 cycles); and

5 Baseline measurement of overall tumour burden is documented (see Note); and

6 Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of pembrolizumab will not be continued beyond 12 weeks (4 cycles) if their disease progresses during this time.

Continuation
Medical oncologist
Re assessment required after 4 months
All of the following:

1 Any of the following:
   1 1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
   1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
   1.3 Patient has stable disease according to RECIST criteria (see Note); and
2 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3 No evidence of progressive disease according to RECIST criteria (see Note); and
4 The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
5 Pembrolizumab is to be used at a maximum dose of 2 mg/kg every 3 weeks for a maximum of 12 weeks (4 cycles)

Notes:
Disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47). Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ) Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements Target lesion measurements should be assessed using CT or MRI imaging with the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

- Complete Response: Disappearance of all target lesions Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
- Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

resolve to amend the Special Authority restrictions applying to nivolumab (Opdivo) in Section B of the Pharmaceutical Schedule from 1 September 2016 as follows (additions in bold):

Special Authority for Subsidy
Initial Application — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1 Patient has metastatic or unresectable melanoma stage III or IV; and
2 Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and
3 Either:
   3 1 Patient has not received funded pembrolizumab; or
   3.2 Both:

3.2.1 Patient has received an initial Special Authority approval for pembrolizumab and has discontinued pembrolizumab within 12 weeks of starting treatment due to intolerance; and

3.2.2 The cancer did not progress while the patient was on pembrolizumab; and

4 Nivolumab is to be used at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 12 weeks (6 cycles); and

5 Baseline measurement of overall tumour burden is documented (see Note); and

6 Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of nivolumab will not be continued beyond 12 weeks **(6 cycles)** if their disease progresses during this time

Renewal application — (unresectable or metastatic melanoma) only from a medical oncologist**.**
Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1 Any of the following:
   1 1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
   1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
   1.3 Patient has stable disease according to RECIST criteria (see Note); and
2 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3 No evidence of progressive disease according to RECIST criteria (see Note); and
4 The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
5 Nivolumab will be used at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 12 weeks (6 cycles)

Notes:
Disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47). Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ) Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements Target lesion measurements should be assessed using CT or MRI imaging with the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

- Complete Response: Disappearance of all target lesions Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
- Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

resolve to amend the restrictions applying to nivolumab (Opdivo) in Part II of Section H of the Pharmaceutical Schedule from 1 September 2016 as follows (additions in bold):

Restricted
Initiation
Medical oncologist
Re assessment required after 4 months
All of the following:

1 Patient has metastatic or unresectable melanoma stage III or IV; and
2 Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and
3 Either:

3.1 Patient has not received funded pembrolizumab; or
3 2 Both:
3.2.1 Patient has received an initial Special Authority approval for pembrolizumab and has discontinued pembrolizumab within 12 weeks of starting treatment due to intolerance; and
3.2.2 The cancer did not progress while the patient was on pembrolizumab; and

4 Nivolumab is to be used at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 12 weeks (6 cycles); and
5 Baseline measurement of overall tumour burden is documented (see Note); and
6 Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of nivolumab will not be continued beyond 12 weeks **(6 cycles)** if their disease progresses during this time.

Continuation
Medical oncologist
Re-assessment required after 4 months
All of the following:

1 Any of the following:
1 1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
1 2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
1.3 Patient has stable disease according to RECIST criteria (see Note); and
2 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3 No evidence of progressive disease according to RECIST criteria (see Note); and
4 The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
5 Nivolumab will be used at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 12 weeks (6 cycles)

Notes:
Disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47). Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ) Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements. Target lesion measurements should be assessed using CT or MRI imaging with the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

- Complete Response: Disappearance of all target lesions Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
- Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

resolve to establish "Programmed cell death-1 (PD-1) inhibitors" as a therapeutic sub group from 1 September 2016 in accordance with section 3.3 of PHARMAC's Operating Policies and Procedures, on the basis that, from the advice we have received, PD 1 inhibitors could be expected to produce the same or similar therapeutic effect;

resolve to list posaconazole tablets modified release 100 mg (Noxafil) in Section B and Part II of Section H of the Pharmaceutical from 1 September 2016 at a price and subsidy of $869 86 per pack of 24 tablets (ex manufacturer, excluding GST);

resolve to list posaconazole tablets modified release 100 mg in Section B and Part II of Section H of the Pharmaceutical Schedule subject to the same Special Authority criteria and hospital restrictions (respectively) that apply to posaconazole oral liquid 40 mg per ml at 1 September 2016;

resolve to approve the 22 June 2016 agreement with Merck Sharp and Dohme (New Zealand) Limited;

note that the above agreement also includes a change in contractual terms for raltegravir 400 mg tablets (Isentress) without any changes to the current Pharmaceutical Schedule listing of this product; and

resolve that the consultation on this proposal was appropriate, and no further consultation is required

SUMMARY OF PROPOSAL				
Market data	**Year ending**	**30 Jun 2017**	**30 Jun 2018**	**30 Jun 2019**
Combined Pharmaceuticals	Subsidy (gross)	Withheld	Withheld	Withheld
	Net cost to Schedule	Withheld	Withheld	Withheld
	Net present value	Withheld under		
	Net distribution costs	With	With	With
	Net cost to DHBs	Withheld	Withheld	Withheld
	Net present value	Withheld under		
Hospital Pharmaceuticals	Expenditure (gross)	Withheld	Withheld	Withheld
	Net cost to DHBs	Withheld	Withhel	Withhel
	Net present value	Withheld		
Other DHB costs	Net cost to DHBs	($450,000)	($740,000)	($810,000)
Total	Total cost to DHBs	Withheld	Withheld	Withheld under
	Net present value	Withheld under		

SUMMARY OF PHARMACEUTICAL: PEMBROLIZUMAB (KEYTRUDA)				
Market data	**Year ending**	**30 Jun 2017**	**30 Jun 2018**	**30 Jun 2019**
Number of patients		318	259	263
Combined Pharmaceuticals	Subsidy (gross)	Withheld	Withheld	Withheld
	Net cost to Schedule	Withheld	Withheld	Withheld
	Net present value	Withheld under		
	Net distribution costs	Wi	Wi	Wi
	Net cost to DHBs	Withheld	Withheld	Withheld
	Net present value	Withheld under		
Other DHB costs	Net cost to DHBs	($450,000)	($740,000)	($810,000)
Total	Total cost to DHBs	Withheld	Withheld	Withheld under
	Net present value	Withheld under		

SUMMARY OF PHARMACEUTICAL: POSACONAZOLE (NOXAFIL)				
Market data	**Year ending**	**30 Jun 2017**	**30 Jun 2018**	**30 Jun 2019**
Combined Pharmaceuticals	Subsidy (gross)	Withheld	Withheld	Withheld
	Net cost to Schedule	Withhel	Withhel	Withhel
	Net present value	Withheld		
	Net distribution costs	With	With	With
	Net cost to DHBs	Withhel	Withhel	Withhel
	Net present value	Withheld		
Hospital Pharmaceuticals	Expenditure (gross)	Withheld	Withheld	Withheld
	Net cost to DHBs	Withheld	Withhel	Withhel
	Net present value	Withheld		
Other DHB costs	Net cost to DHBs	$0	$0	$0
Total	Total cost to DHBs	Withheld	Withheld	Withheld
	Net present value	Withheld		

Notes:
1. Subsidy (gross) and expenditure (gross) = forecast of spending at the proposed price and subsidy.
2. Net cost to DHBs = forecast of change in spending compared with status quo
3 All pharmaceutical costs are ex-manufacturer
4. All costs are ex-GST.
5. NPV is calculated over 5 years using an annual discount rate of 8%.
6. Calculations are in A926755.

Executive Summary

- The PHARMAC Board recently made a decision to fund nivolumab (Opdivo), a programmed cell death 1 (PD 1) inhibitor, for patients with unresectable or metastatic (stage III or IV) melanoma (advanced melanoma) from 1 July 2016

- During consultation on the nivolumab listing, we received a consensus statement from a number of medical oncologists, who told us that, in their view, nivolumab and pembrolizumab are considered clinically similar to the extent that they were comfortable switching patients from one treatment to the other

- During this time we also took advice from PTAC, which noted that the currently available evidence is consistent with different PD 1 inhibitors (i e pembrolizumab and nivolumab) having similar efficacy.

- PHARMAC has now reached a commercially favourable provisional agreement with Merck Sharpe and Dohme (New Zealand) Limited (MSD) for the supply of another PD-1 inhibitor, pembrolizumab (Keytruda). The agreement includes three components, all of which, if approved, would take effect from 1 September 2016:

    - funding of pembrolizumab as an additional first-line treatment option for patients with advanced melanoma, subject to Special Authority criteria and hospital restrictions essentially the same as those applying to nivolumab A confidential rebate would apply but there would be no protection from subsidy reduction or delisting;

    - funding of a modified-release tablet form of the antifungal agent posaconazole (Noxafil), in addition to the oral liquid form which is already funded, with subsidy and delisting protection until 30 June 2019. A confidential rebate would apply; and

    - provision of subsidy and delisting protection for posaconazole oral liquid (Noxafil) and raltegravir (Isentress) until 30 June 2019, without changing the listings of these treatments.

- Separate to the provisional agreement with MSD we are also proposing to, from 1 September 2016:

    - amend the Special Authority criteria applying to nivolumab to allow switching between nivolumab and pembrolizumab for patients who experience early treatment intolerance on their first treatment; and

    - establish “programmed cell death 1 (PD 1) inhibitors” as a therapeutic sub group as defined in PHARMAC’s Operating Policies and Procedures.

- Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j)
  Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j)
  Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j) The proposal would also provide an estimated additional savings to DHB hospitals of Withheld under section 9(2)(b)(ii) (5-year NPV, 8%) associated with reduced infusion costs, bringing the total savings to DHBs to Withheld under section 9(2)(b)(ii) over 5 years (NPV, 8%)

- The proposal to fund posaconazole tablets would provide a useful clinical alternative to posaconazole oral liquid and would result in a net cost of Withheld to the CPB, a net cost of Withheld to DHB hospitals, and a net overall cost of Withheld to DHBs including distribution costs (5 year NPV, 8%)

- The proposal to amend the subsidy and delisting protection for posaconazole oral liquid and raltegravir tablets would have minimal financial impact and no clinical impact

- The combined impact of the proposal to fund pembrolizumab and the proposal to amend the nivolumab criteria is an estimated increase in use of funded PD 1 inhibitors of approximately 7%, which would result from people who otherwise would have stopped treatment due to intolerance being able to try another funded treatment. This increase has been taken into account in the overall budget impact of funding pembrolizumab. With

Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j)

Withheld under section

- Establishment of PD-1 inhibitors as a therapeutic sub group would not only create future opportunity for savings in this market but would provide clear visibility to the supply market about PHARMAC's view on the similarity of these treatments

Why Proposal Not Decided Under Delegated Authority

The proposal outlined in this Board paper has not been dealt with by the Chief Executive under delegated authority because the estimated Financial Impact (NPV) of this proposal is more than $10,000,000 of the Pharmaceutical Budget The Financial Impact (NPV) is calculated on the basis of the net present value of the proposed subsidy (ex-manufacturer exclusive of GST) over 5 years at a discount rate of 8% to be paid by the funder for the product(s) and the forecast demand, taking into account any effect of the change /decision on that demand, versus the status quo.

The Proposal

There are three components to the proposal

The first involves an agreement with MSD to:

- fund pembrolizumab as an additional first line treatment option for patients with advanced melanoma, subject to Special Authority criteria and hospital restrictions essentially the same as those applying to nivolumab from 1 September 2016. The proposed criteria would permit funded access to pembrolizumab for patients who experience early treatment intolerance on first line funded nivolumab. A confidential rebate would apply but there would be no protection from subsidy reduction or delisting;

- fund a tablet form of the antifungal agent posaconazole (Noxafil) from 1 September 2016, in addition to the oral liquid form which is already funded, subject to the same Special Authority criteria and hospital restrictions as posaconazole oral liquid. Both presentations would have subsidy and delisting protection until 30 June 2019 and a confidential rebate would apply to both presentations; and

- provide subsidy and delisting protection for raltegravir (Isentress) from 1 September until 30 June 2019, without changing the listing of this treatment.

Note: an agreement, conditional on consultation and Board approval, between Merck Sharp and Dohme (New Zealand) Limited and PHARMAC dated 22 June 2016 is attached as Appendix 1

The second component to the proposal is to amend the Special Authority criteria applying to nivolumab from 1 September 2016 so that it would also be funded for patients who experience early treatment intolerance on first-line funded pembrolizumab.

The third component of the proposal is to establish "programmed cell death 1 (PD 1) inhibitors" as a therapeutic sub-group as defined in PHARMAC's Operating Policies and Procedures from 1 September 2016.

Further Information

Pembrolizumab

The proposal to fund pembrolizumab is a result of evolving information and proposals over time and is best summarised as a sequence of specific phases.

- In September 2015, we received an application to fund pembrolizumab. The clinical evidence that accompanied this application signalled a clinical benefit (tumour response) but not a survival gain The proposal from the supplier was also extremely expensive. The funding application was reviewed by the Pharmacology and Therapeutics Advisory Committee (PTAC) and the Cancer Treatments Subcommittee of PTAC (CaTSoP), which both gave it a low funding priority. They noted that the low priority rating was influenced by the early evidence base, and consequent uncertainty about pembrolizumab's longer term benefits and potential risks, as well as its very high cost
- Pembrolizumab remained under review and PHARMAC staff continued discussions with MSD over potential listing terms and pricing

- In April 2016, PHARMAC received a funding application from Bristol Myers Squibb (BMS) to fund nivolumab The evidence for this treatment at that time was stronger than for pembrolizumab, as it showed some survival gain.
- PHARMAC staff also entered into discussions with BMS over potential listing terms and pricing for nivolumab following registration. Nivolumab was registered on 28 April 2016
- In late April 2016 the PHARMAC Board reviewed the clinical advice and considered the commercial terms that had been negotiated with BMS and MSD. The Board directed PHARMAC staff to re negotiate on pembrolizumab, seeking improved commercial terms that take into account the changed circumstances arising from the commercial proposal for nivolumab, and the more favourable clinical data and expert advice for nivolumab At the time, the key benefit of the nivolumab provisional agreement from commercial/future strategic perspective was that it did not include subsidy or delisting protection and PHARMAC would have total discretion with respect to the nivolumab access criteria, Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j)
- On 4 May 2016 we consulted on funding nivolumab for advanced melanoma.
- During consultation on the nivolumab listing, we received a consensus statement from 13 medical oncologists, from across all New Zealand cancer centres, who regularly manage melanoma patients They told us that, in their view, nivolumab and pembrolizumab are considered clinically similar to the extent that they were comfortable switching patients from one treatment to the other.
- During this time we also took further advice from PTAC (May 2015), which noted that the currently available evidence is consistent with different PD 1 inhibitors (i.e. pembrolizumab and nivolumab) having similar efficacy This view was also supported by CaTSoP.
- In June 2016 we reached a provisional agreement with MSD Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j). The provisional agreement does not contain subsidy or delisting protection and PHARMAC would have total discretion with respect to pembrolizumab access criteria. As part of the negotiation we also agreed to include two other products in the provisional agreement (posaconazole and raltegravir), discussed further below

More information about the proposal to fund pembrolizumab is included in the assessment of the proposal against the Factors for Consideration, below.

Nivolumab

Nivolumab has been funded since 1 July 2016 subject to Special Authority criteria for patients with advanced melanoma. The proposed changes are to enable funding of nivolumab for patients who experience treatment intolerance on first line funded pembrolizumab and their cancer has not progressed while taking funded pembrolizumab. This change would only be relevant if the proposal to fund pembrolizumab is approved.
We note that the alternative option would be to prevent patients from being able to switch treatments on early intolerance; ie patients would have access to only one of two funded treatments. However, we consider that there is some merit in permitting treatment switching due to early intolerance in that it would lend weight to the notion that clinicians are comfortable switching patients from one treatment to the other and it could provide us with some valuable data on the actual incidence of early intolerance and the likelihood of this

being a class effect common to both treatments (as is posited in one of the consultation responses)

Note that if PHARMAC was to adopt a commercial strategy in the future that would result in only one PD 1 inhibitor being funded (or only one being fully funded), this would remove the option of switching between treatments on early intolerance. Collection of switching data would help assist in assessment of the impact of implementing any such strategy.

The financial impact of the proposed change, which would result in additional PD-1 inhibitor being funded (ie pembrolizumab) for a small proportion of people who otherwise would have stopped treatment due to intolerance, is taken into account in the financial impact analysis for the proposed pembrolizumab listing and is discussed further in that context.

With the exception of the financial impact, this aspect of the proposal is not discussed further in this decision paper.

Establishment of PD 1 inhibitors as a therapeutic subgroup

A therapeutic sub-group is defined in PHARMAC's Operating Policies and Procedures as a set of pharmaceuticals that produce the same or similar therapeutic effect in treating the same or similar condition(s).

Recent advice from PTAC (May 2016) is that, although there are no head-to-head studies, the currently available evidence is consistent with different PD 1 inhibitors (ie pembrolizumab and nivolumab) having similar efficacy. This view is supported by medical oncologist feedback we received in response to consultation on the proposal to fund nivolumab.

Feedback from 13 New Zealand medical oncologists (from all cancer centres), who regularly manage melanoma and many of whom have treated patients with pembrolizumab or nivolumab in clinical trials or access programmes or in the private sector,, told us that, in their view, nivolumab and pembrolizumab are considered clinically similar to the extent that they were comfortable switching patients from one treatment to the other.

This view is also supported by CaTSoP, which advised that: "based on the currently available evidence, noting the difference in trial design and absence of head to head comparative data, that pembrolizumab and nivolumab appeared to be mechanistically similar and were considered to provide the same or similar therapeutic effect in the treatment of advanced melanoma to the extent that it would be reasonable to run a competitive process that would result in only one PD 1 inhibitor being funded " (excerpt from draft minute from April 2016 CaTSoP meeting)

[redacted] PD 1 inhibitors remain expensive treatments that are also likely to be registered to treat other types of cancer in the future Given current and future competition in this market, we consider that it is important to be able to create opportunities for future savings

Establishing a "PD 1 inhibitors" therapeutic sub-group would more readily enable reference pricing to be applied to this therapeutic sub-group in the future Reference pricing means that all pharmaceuticals in any given therapeutic sub-group would be subsidised at the level of the lowest priced pharmaceutical in that sub group PHARMAC would consult before making any decisions about reference pricing in this therapeutic sub-group.

The relevant excerpt from PHARMAC's Operating Policies and Procedures is as follows:

3.3 Definitions of reference pricing and therapeutic groupings

3 3 1 Subject to clause 3 1, reference pricing means that all pharmaceuticals in any given therapeutic sub-group to which PHARMAC decides to apply reference pricing are subsidised at the level of the lowest priced pharmaceutical in that sub-group Reference pricing is based on the classification of pharmaceuticals into different therapeutic groups and further into sub-groups

3.3.2 A **therapeutic group** is defined as a set of pharmaceuticals that are used to treat the same or similar condition(s) A **therapeutic sub-group** is defined as a set of pharmaceuticals that produce the same or similar therapeutic effect in treating the same or similar condition(s)

3.3.3 PHARMAC will carry out appropriate consultation on the classification of pharmaceuticals into therapeutic sub groups and its application of reference pricing in respect of a particular sub-group.

3 3 4 PHARMAC is not bound to apply reference pricing in every situation, or in the same way in every situation, where pharmaceuticals have been classified into a therapeutic sub-group. PHARMAC may also provide exemptions from reference pricing to certain pharmaceuticals, or groups of pharmaceuticals or to groups of patients, provided that PHARMAC consults on any proposed exemption before making its decision

3.3.5 PHARMAC may, on the advice of PTAC, change the status of a pharmaceutical within a particular therapeutic sub group, or revise the composition of a therapeutic sub group, in light of new knowledge about that pharmaceutical or the pharmaceuticals within that sub-group

3.3.6 In the event that PHARMAC decides to apply reference pricing to any particular hospital pharmaceuticals it would envisage (subject to consultation if any alternative is proposed) using existing definitions for more information on the creation of therapeutic sub-groups and reference pricing

This aspect of the proposal in and of itself would have no clinical or financial impact and is not discussed further in this decision paper.

Posaconazole tablets

Posaconazole (Noxafil) modified-release tablets and oral liquid are indicated for use in the treatment of invasive fungal infections in patients 18 years of age or older

Posaconazole oral liquid 40 mg per ml is currently funded subject to Special Authority criteria for patients with acute myeloid leukaemia treated with high-dose chemotherapy and for patients with a stem cell transplant and graft versus host disease on significant immunosuppressive therapy.

This proposal would see a tablet form of the same treatment available for the same patient group.

Further information is included in the assessment of the proposal against the Factors for Consideration, below, where relevant

Raltegravir tablets

Raltegravir (Istentress) is an integrase strand transfer inhibitor that is indicated, in combination with other antiretroviral agents, for the treatment of human immunodeficiency virus (HIV 1) infection Raltegravir tablets are funded subject to the same Special Authority criteria that apply to other HIV treatments. Isentress is a twice daily formulation.
The main impact of extending the subsidy and delisting protection for raltegravir (Isentress) to 30 June 2019 would be to limit PHARMAC's ability to leverage competition for raltegravir tablets. However, while we consider that the proposal would somewhat reduce our ability to

realise savings from a direct competitor to twice daily raltegravir, we consider that we would still have sufficient alternative options to promote competition for two key reasons:

- There is competition from once daily formulations of alternative integrase strand transfer inhibitor formulations such as dolutegrevir (GSK) and elvitegravir (Gilead) Our clinical advice indicates that the availability of the once daily formulation would result in the whole strand transfer market shifting from raltegravir to a once daily formulation.

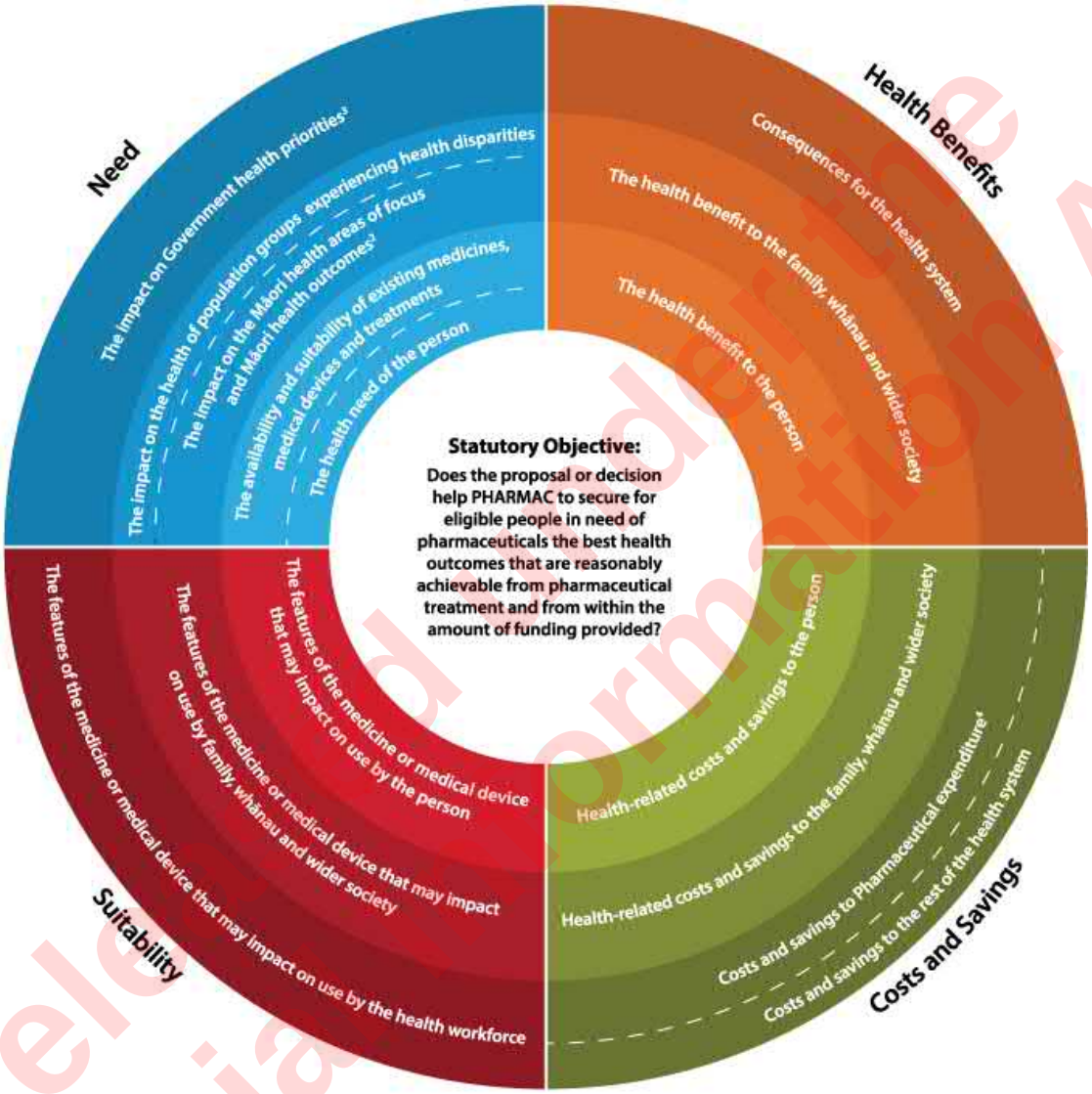
- We would retain the ability to keep Isentress on its existing Special Authority while listing a competitor under a different Special Authority with wider access. This would likely result in all new patients accessing the wider access treatment

For these reasons, we expect that this aspect of the proposal would have minimal financial impact There would be no clinical impact as no changes are proposed to the listing of raltegravir.

This aspect of the proposal is not discussed further in this decision paper

Factors for Consideration

This paper sets out PHARMAC staff's assessment of the proposal using the Factors for Consideration in the Operating Policies and Procedures Some Factors may be more or less relevant (or may not be relevant at all) depending on the type and nature of the decision being made and, therefore, judgement is always required The Board is not bound to accept PHARMAC staff's assessment of the proposal under the Factors for Consideration and may attribute different significance to each of the Factors from that attributed by PHARMAC staff.



Footnotes

[1] The person receiving the medicine or medical device must be an eligible person, as set out in the Health and Disability Services Eligibility Direction 2011 under Section 32 of the New Zealand Public Health and Disability Services Act 2000

[2] The current Māori health areas of focus are set out in PHARMAC's Te Whaioranga Strategy.

[3] Government health priorities are currently communicated to PHARMAC by the Minister of Health's Letter of Expectations.

[4] Pharmaceutical expenditure includes the impact on the Combined Pharmaceutical Budget (CPB) and / or DHB hospital budgets (as appropriate).

5 Please note PHARMAC's Factors for Consideration schematic currently does not explicitly refer to the health needs of family, whānau and wider society, but this factor should be considered alongside those depicted in the schematic

Factors for Consideration

Health need

Disease/illness

Pembrolizumab

Melanoma is a malignant tumour of melanocytes; the cells that produce dark skin pigmentation. Melanomas predominantly occur in skin, but can be found in other parts of the body, including the bowel and the eye Melanoma is less common than other skin cancers (e.g. squamous and basal cell carcinomas); however, it is the most aggressive.

New Zealand has the highest melanoma incidence rate in the world Melanoma is the fourth most common cancer in NZ: the New Zealand Cancer registry records that in 2012, 2,324 people were diagnosed with melanoma and there were a total of 354 deaths from melanoma (222 in men, 132 in women) The majority of melanoma cases, around 70%, occur in people aged 50 years and older. Melanoma rates in NZ are increasing: between 1998 and 2008 the rates of melanoma diagnosis increased by 12 and 16 percent for males and females, respectively

Early diagnosis and treatment is the key to minimising morbidity and mortality in patients with melanoma The majority of patients with localised disease can be cured with surgical resection; however, some patients present with, or subsequently develop, advanced disease.

The prognosis for patients with advanced/metastatic (stage IV) melanoma if left untreated is poor: the majority of patients will die within a year of diagnosis, with 5 year overall survival rates approximately 15% 20% and 10 year survival rates approximately 10% 15%

Posaconazole

Posaconazole is an extended spectrum triazole antifungal with activity against Aspergillus spp and the agents of mucormycosis. An oral liquid formulation of posaconazole is funded for prophylaxis of invasive fungal infections in high risk/immunocompromised individuals (acute myeloid leukaemia treated with high dose chemotherapy and for patients with a stem cell transplant and graft versus host disease on significant immunosuppressive therapy)

Invasive fungal infections are common in high risk patients on significant immunosuppressive treatment and with haematologic malignancies, such as patients with acute leukaemia receiving induction chemotherapy, and cause substantial morbidity and mortality. The risk of invasive fungal infections increases with the duration and severity of neutropenia, prolonged antibiotic use, and number of chemotherapy cycles. In patients with acute myelogenous leukaemia, the incidence of invasive aspergillosis has ranged from 2 to 28%, with most studies reporting rates between 5 and 10%

Availability and suitability of existing treatments

Pembrolizumab

Currently funded treatment options for advanced/metastatic melanoma include palliative radiation, chemotherapy treatment (dacarbazine) and, from 1 July 2016, nivolumab.

Dacarbazine

The efficacy of dacarbazine (also known as DTIC) is limited A pooled analysis of 23 randomised, controlled trials reported that the objective response rate for 1,390 patients receiving dacarbazine alone was 15.3%. The majority of these responses were partial (11 2% partial responses, 4 2% complete responses) (Lui et al Cancer Treat Rev 2007;33:665–680). Where patients do respond to dacarbazine, responses are usually partial and of short duration, with median response duration of four to six months. Since dacarbazine monotherapy has not been investigated in a placebo-controlled trial, there is insufficient evidence to suggest an overall survival benefit with dacarbazine. Dacarbazine is generally well tolerated, with the major side effect being nausea and vomiting Bone marrow suppression is usually modest, and alopecia and fatigue are minimal, allowing most patients to maintain relatively normal function while receiving therapy.

Nivolumab

Nivolumab is a fully human immunoglobulin (IgG4) monoclonal antibody which binds to the PD-1 receptor on the surface of T-cells and blocks its interaction with programmed death-ligand 1 (PD L1) and PD L2 expressed by antigen presenting cells and other cells such as tumour cells The PD 1 receptor is a protein located on T-cells and pro B cells which interacts with its ligands to inhibit T-cell activation and proliferation, thereby down-regulating the immune system. Through this mechanism of action, PD 1 inhibitors have the potential to treat a broad range of tumour types.

The recommended dose of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks.

The key evidence for nivolumab as monotherapy for the treatment of advanced melanoma comes from CheckMate-066, a randomised, placebo controlled, double blind, phase III study of nivolumab compared with dacarbazine in previously untreated patients with metastatic melanoma without a BRAF mutation.

Currently published evidence from this study reports nivolumab as monotherapy providing a median progression-free survival of 5.1 months compared with 2.2 months with dacarbazine (Robert et al NEJM 2015;372:320 30). Survival results, at a median follow up of 18.5 months, reported that median overall survival was not reached in the nivolumab arm compared with 11.0 months for patients treated with dacarbazine (Atkinson et al SMR 2015 poster presentation). The reported overall survival rate at one year was 73% with nivolumab compared to 42% with dacarbazine, and the two year rate was reported as 57% compared to 26% respectively. The objective response rate with nivolumab was 40% compared to 14% with dacarbazine.

Nivolumab is general well tolerated, with a small number of significant immunologically mediated side effects.

Posaconazole

Posaconazole oral liquid is currently funded for the relevant indications This is the same chemical as the proposed new listing, just a different formulation The Haematology Subcommittee (August 2012) has previously advised that posaconazole is effective in reducing the incidence of invasive fungal infections in immunocompromised patients and recommended it be funded for these patients.

Health need of others

Pembrolizumab

We are not aware of any significant health impact on others from patients with advanced melanoma.

Posaconazole

It is possible that if immunocompromised patients contract an invasive fungal infection this could be transmitted to others; however, given that posaconazole is already funded for this indication this is unlikely to be hugely relevant to the proposal.

Impact on Māori health areas of focus and health outcomes

Pembrolizumab

Māori and Pacific peoples have a significantly lower incidence of melanoma compared with the New Zealand population as a whole However, Māori and Pacific peoples have a relatively higher rate of nodular melanoma, which is an invasive form of melanoma that has an increased risk of metastasis and, therefore, worse prognosis.

Posaconazole

None noted as being relevant to this proposal

Any other populations experiencing health disparities

None noted as being relevant to this proposal.

Government health priorities

Pembrolizumab

“Shorter waits for cancer treatment / Faster cancer treatment” is a Government Health Target. Pembrolizumab is delivered by intravenous infusion which would impact on DHB infusion and associated care capacity (which are currently heavily constrained) as well as the limited number of medical oncologists within DHB hospitals. However, given that pembrolizumab has a shorter infusion time (30 minutes versus 60 minutes for nivolumab) and less frequent dosing schedule (every three weeks versus every two weeks for nivolumab), funding of pembrolizumab could decrease waiting times and have a positive impact on this Health Target relative to the current situation with nivolumab.

Posaconazole

None noted as being relevant to this proposal.

Health Benefit

Clinical advice and evidence

Pembrolizumab

Pembrolizumab is indicated as monotherapy for the treatment of unresectable or metastatic melanoma in adults The recommended dose of pembrolizumab is 2 mg/kg administered intravenously over 30 minutes every three weeks until disease progression or unacceptable toxicity.

Following its approval by Medsafe on 3 September 2015, the pembrolizumab (Keytruda) funding application was first assessed by CaTSoP in September 2015 and then by PTAC in November 2015 Both committees recommended that pembrolizumab be funded for the treatment of advanced melanoma with a low priority. They noted that the low priority rating was influenced by the early evidence base, and consequent uncertainty about pembrolizumab's longer term benefits and potential risks, as well as its very high cost Uncertainty around the optimal dosing regimen was also noted. Collated CaTSoP and PTAC minutes for pembrolizumab can be found in Appendix 2

The current clinical trial evidence for pembrolizumab in advanced melanoma comprises one Phase I trial, one open label Phase II/III trial and one open-label Phase III trial:

- Keynote-001 (Hamid et al. N Engl J Med. 2013;369:134-44; Robert et al. Lancet. 2014;384:1109–17) was an open label Phase I trial that included both advanced lung cancer and melanoma patients and looked at various doses of pembrolizumab. There was no comparator treatment or control group in this study. PTAC noted that results of the primary efficacy measure in Keynote 001 of overall response rate (ORR) varied across the dosing cohorts and patient populations examined. Robert et al. reported an ORR of 26 % in a pooled analysis of ipilimumab refractory advanced melanoma patients treated with pembrolizumab at doses of 2 mg/kg or 10 mg/kg every 3 weeks Unpublished evidence provided by the supplier reported an ORR of between 31 and 44% in ipilimumab-naïve patients across the dosing cohorts Hamid et al reported an ORR of 52% in the pooled population of ipilimumab-naïve and pre-treated patients receiving the 10 mg/kg every 2 weeks regimen. Median progression free survival (PFS) ranged from 3.3 months for ipilimumab-refractory patients treated with pembrolizumab at 2 mg/kg every 3 weeks to 8.7 months for ipilimumab-naive patients treated with pembrolizumab at 10 mg/kg every 2 weeks.

- Keynote-002 (Ribas et al. Lancet Oncol 2015;16:908–18) was an open-label Phase II/III trial that compared two different doses of pembrolizumab treatment with standard chemotherapy treatment (paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or temozolomide) in patients with advanced melanoma whose disease had progressed following prior treatment with ipilimumab. This trial enrolled patients with advanced melanoma who had previously been treated with ipilimumab and/or a BRAF inhibitor. Median PFS was 2.9 months in both of the pembrolizumab groups compared with 2.7 months in the investigator choice chemotherapy treatment group. However, because the first tumour assessment was conducted at 12 weeks and more than half of

the patients in each treatment group had progressed at this time, PTAC considered that these results were likely confounded by timing of the assessment

- Keynote-006 (Robert et al. N Engl J Med. 2015;372:2521 32) was an open label randomised controlled Phase III trial for pembrolizumab which compared two different doses of pembrolizumab with ipilimumab treatment in patients with advanced melanoma. This trial enrolled patients with advanced melanoma who had not received any previous treatment or who had previously been treated with ipilimumab and/or a BRAF inhibitor Median PFS, the primary endpoint of the study, was 5.5 months (pembrolizumab 10 mg/kg every 2 weeks), 4.1 months (pembrolizumab 10 mg/kg every 3 weeks), and 2.8 months (ipilimumab) respectively Median overall survival (OS) was not reached in any of the arms, but hazard ratios for death for the two pembrolizumab regimens were 0.63 (95% CI 0.47 to 0.83), P<0.0005, and 0.69 (95% CI 0.52 to 0.90), P = 0.0036, compared to ipilimumab Response rates were 34% for pembrolizumab 10 mg/kg every 2 weeks arm (P<0.001 compared to ipilimumab), 33% for pembrolizumab 10 mg/kg every 3 weeks arm (P<0 001 compared to ipilimumab), and 12% for ipilimumab arm Complete responses were seen in 5%, 6% and 1.4% of these patients respectively. Of the 34%, 33% and 12%, respectively, of patients who responded to treatment in each group, responses were ongoing in 89%, 97%, and 88% of patients, respectively, at the time of the analysis (median follow up of 7 9 months). PTAC considered that these results indicated that between 30% and 32% of all patients treated with pembrolizumab at 10 mg/kg experienced a durable response within the time frame of follow up in the report, i.e. response ongoing at 7.9 months median follow-up, with between 1% and 4% experiencing only a short term response and the remaining two-thirds, between 66% and 67% of patients, having no response to pembrolizumab treatment. Grade 3 to 5 severe adverse events occurred in 13% and 10% of patients in the pembrolizumab groups compared with 20% in the ipilimumab group.

There has been no further published evidence for pembrolizumab since the November 2015 PTAC review. However, our current view is that, given the advice from PTAC (May 2016) and CaTSoP (April 2016) regarding the class of PD-1 inhibitor treatments, it is reasonable to assume that the overall survival benefit seen with nivolumab (OS rate at one year was 73% compared to 42% with dacarbazine, and the two year rate was 57% compared to 26%, respectively) would be realised with pembrolizumab We will continue to review new published evidence for both treatments as it becomes available.

Posaconazole

In November 2015 the Anti-infective Subcommittee of PTAC provided the following advice in relation to posaconazole modified release tablets:

1.1 The Subcommittee noted that PHARMAC has received a commercial proposal from a supplier for posaconazole modified release tablets.

1 2 The Subcommittee noted that there are a number of issues related to the use of posaconazole liquid including palatability and the requirement that it is taken with a high-fat meal. The Members considered that a number of these issues could be overcome with the introduction of a modified release tablet However the Subcommittee emphasised that a liquid formulation should remain available for paediatric use.

Health benefit to others

None noted as being relevant to this proposal

Consequences for the health system

Pembrolizumab

This proposal would require administration of pembrolizumab intravenous infusions in DHB hospitals There are finite infusion services and associated care capacity as well as a limited number of medical oncologists within DHB hospitals. Given the shorter infusion time and less frequent dosing schedule compared with nivolumab, the listing of pembrolizumab would likely have a positive impact on the burden (both financial and resource) on infusion services versus the status quo of nivolumab only. This is discussed further in more detail under the costs and savings Factors below.

Suitability

Pembrolizumab

As noted above, pembrolizumab has a shorter infusion time and less frequent dosing schedule (30 minutes every three weeks) compared with nivolumab (60 minutes every two weeks), which would likely be preferred by both patients and DHBs

In addition, the proposal would provide a second option for people who experience early treatment limiting side effects from nivolumab.

The common side effects of nivolumab are listed on the Medsafe Consumer Medicine Information sheet as:

- Problems with the lungs such as breathing difficulties, or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease)
- Diarrhoea (watery, loose or soft stools) or any symptoms of inflammation of the intestines (colitis), such as stomach pain and mucus or blood in the stool.
- Inflammation of the liver (hepatitis).Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of the stomach area, or tiredness.
- Inflammation or problems with the kidneys. Signs and symptoms may include abnormal kidney function tests decreased volume of urine, and kidney failure.
- Problems with the hormone producing gland (including the thyroid, pituitary, and adrenal glands) that may affect how these glands work Signs and symptoms that the glands are not working properly may include fatigue (extreme tiredness), weight change or headache and visual disturbances
- Diabetes (symptoms include excessive thirst, the passing of a greatly increased amount of urine, increase in appetite with a loss of weight, feeling tired, drowsy, weak, depressed, irritable and generally unwell) or diabetic ketoacidosis (acid in the blood produced from diabetes).
- Inflammation of the skin that can lead to rash and itching. Severe peeling of the skin.

These side effects are very similar to those listed on the pembrolizumab Medsafe Consumer Medicine Information sheet:

- Signs and symptoms of lung problems: shortness of breath, chest pain, coughing
- Signs and symptoms of problems with your intestines: diarrhoea or more bowel movements than usual, your stools are black, tarry, sticky or have blood or mucus, severe stomach pain or tenderness
- Signs and symptoms of liver problems: nausea or vomiting, feeling less hungry, pain on the right side of your stomach , your skin looks yellow, the whites of your eyes look yellow, dark urine, you bleed or bruise more easily than normal
- Signs and symptoms of kidney problems: changes in the amount or colour of your urine
- Signs and symptoms of hormone gland problems (especially the thyroid, pituitary, and adrenal glands): rapid heart beat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, your voice gets deeper, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache
- Signs and symptoms of blood sugar problems: feeling more hungry or thirsty, needing to urinate more often, weight loss
- Signs and symptoms of problems in other organs: Rash, Muscle pain or weakness, Changes in eyesight, Inflammation of the pancreas
- Signs and symptoms of infusion (IV) reactions: Shortness of breath, itching or rash, dizziness, fever

Note that consultation feedback suggests that people may experience similar toxicities if they switch from one PD-1 inhibitor to another as it is likely that most of the side effects are class effects related to PD-1 inhibition.

Posaconazole

A modified release tablet form of posacanazole could help overcome a number of issues related to the use of posaconazole liquid including palatability and the requirement that it is taken with a high fat meal, as advised by the Anti infective Subcommittee of PTAC Posaconazole modified-release tablets are therapeutically equivalent to the oral liquid when taken in a fed or fasting state and they may be taken with or without food

Costs and Savings

Health related costs and savings to the person.

Pembrolizumab

If patients used pembrolizumab instead of nivolumab there would be fewer hospital visits and potentially less time in the hospital per visit; however, this is uncertain and the potential savings to the person are difficult to quantify

Health related costs and savings to the family, whānau and wider community.

Pembrolizumab

We consider that there would be little incremental cost or savings to the family, whānau and wider community associated with pembrolizumab compared with nivolumab.

Cost and savings to pharmaceutical expenditure and the rest of the health system

Pembrolizumab

The estimated pharmaceutical costs and savings and service impacts for pembrolizumab were conducted against the nivolumab analysis, which is itself an estimate As such, there is a high degree of uncertainty around the pembrolizumab analysis. A summary of the nivolumab estimates (patient numbers, infusions) is provided in Appendix 3.

The two key impacts of the proposal are on the pharmaceutical costs and on the infusion costs. The analysis includes the following assumptions and amendments to the nivolumab analysis:

- That 20% of people who would otherwise have started on nivolumab on 1 July 2016 would delay starting on a funded PD 1 inhibitor until 1 September 2016 if they thought pembrolizumab would be funded from 1 September.
- That from 1 September 2016 70% of people would take pembrolizumab and 30% would take nivolumab.
- That the ability to switch between treatments on early toxicity would result in a 7% increase in funded PD-1 use.
- That there would be no increase in the number of patients accessing funded PD 1 inhibitor treatment
- That the mean duration of treatment with pembrolizumab would be the same as for nivolumab; in other words, assumes that survival gains would be the same on each treatment

Note that the estimate of 20% delaying starting on funded treatment until 1 September 2016 is likely an underestimate given that MSD has offered to provide free stock from 1 July 2016 to 1 September 2016. Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j) Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j)

In addition, if the majority of early treatment limiting toxicity is PD-1 inhibitor class related, there would be less increase in use from treatment switching than we have estimated as the second treatment would likely be stopped early as well.

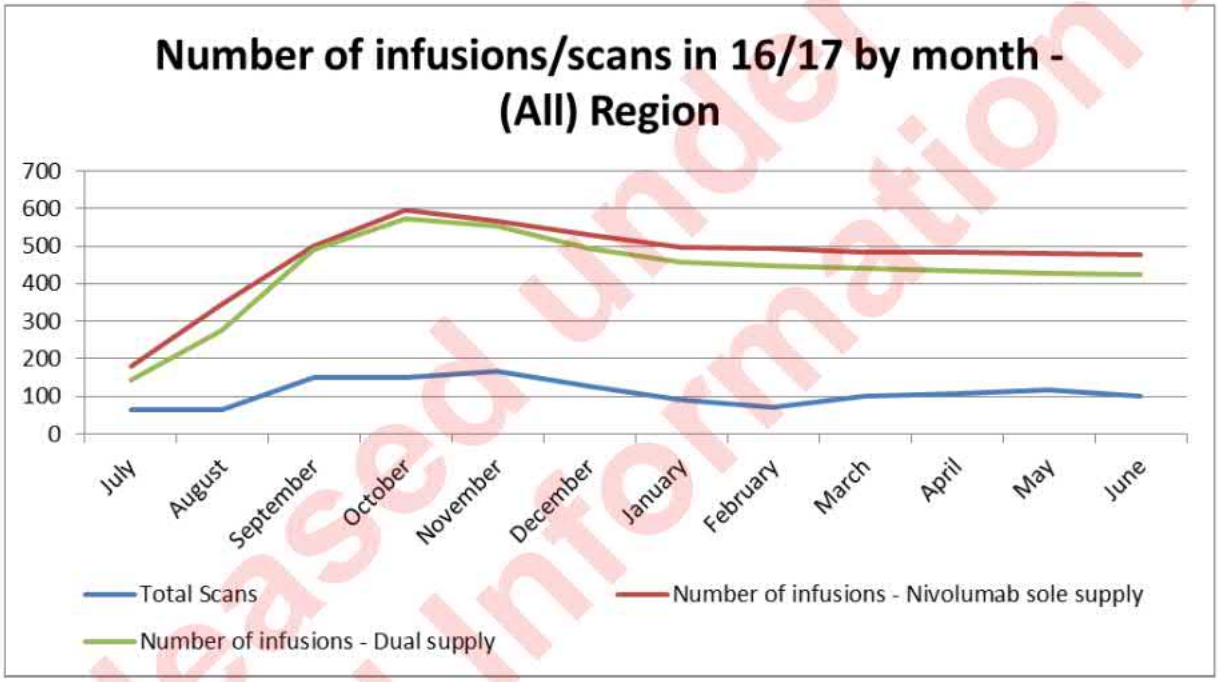
Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j)
Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j)
Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j)
Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and The proposal would also provide an estimated additional savings to DHB hospitals of Withheld under (5-year NPV, 8%) associated with reduced infusion costs, bringing the total savings to Withheld under over 5 years (NPV, 8%).

The following table and graph outlines the number of infusions in Year 1 for each Regional Cancer Network and nationally if nivolumab is the only PD1 inhibitor funded for the treatment of advanced melanoma compared to a scenario where pembrolizumab is funded for 70% of patients with advanced melanoma from 1 September 2016

Regional Cancer Network infusions sole supply or dual supply scenarios, Year 1

Regional Network	Cancer	Number of Infusions (nivolumab only)	Number of Infusions (nivolumab and pembrolizumab)	Percentage of total national patients
Northern		1878	1723	33%
Midland		989	908	18%
Central		1303	1196	23%
Southern		1458	1339	26%
Total		**5628**	**5166**	**100%**

Total number of patients by month accessing funded nivolumab or pembrolizumab in sole supply or dual supply scenarios in Year 1



Posaconazole

The pricing proposed for posaconazole modified release tablets would be Withheld under the currently funded oral liquid with the exception of the first day of dosing, which would be an extra $108.73 per patient associated with the recommended loading dose of an extra 300 mg dose on day one.

There are approximately 80 90 new patients each year taking posaconazole, with a resultant maximum net cost of Withheld to DHBs (5-year NPV, 8%), Withheld of which would be a cost to the CPB. The analysis assumes that 80% of patients would switch to the tablet form and that there would be no savings from reduced wastage associated with the current original pack (OP) dispensing rule for the oral liquid (our data indicate that wastage is currently minimal). The actual cost could be less than this estimate if fewer patients take the tablets instead of the liquid and if there are any savings from reduced liquid wastage

Note that this cost of posaconazole is in the context of an overall savings bundle proposal, and would have a negligible impact on the overall savings

Cost-Effectiveness

Pembrolizumab

The proposal to fund pembrolizumab Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j) Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) would slightly increase patient benefits because of the difference in infusion schedules In cost effectiveness terms, it Withheld under section the current listing of nivolumab, meaning that Withheld under section 9(2)(b)(ii), 9(2)(ba)(i), and 9(2)(i)

However, for completeness we have also presented below a summary of the cost-effectiveness results for pembrolizumab in the absence of nivolumab

Relative to dacarbazine, the cost effectiveness of pembrolizumab for patients with advanced melanoma at the proposed price, in the absence of nivolumab, is estimated to be approximately Wit quality adjusted life years (QALYs) gained per $1 million invested (Withheld per QALY), with a likely range of Withheld QALYs per $million (Withheld under section 9(2) per QALY).

This compares with the analysis for nivolumab considered at the 8 June 2016 Board meeting, which estimated its cost-effectiveness to be approximately Wit QALYs gained per $1 million invested (Withheld per QALY), with a range of Withheld QALYs per $million (Withheld Withheld under per QALY)

The Technology Assessment Report for pembrolizumab in the absence of nivolumab can be provided at Board members' request.

Posaconazole

A CUA has not been conducted for the proposal for posaconazole modified release tablets as, although this component of the proposal would be a small cost, it is in the context of an overall Withheld bundle.

Comments from Interested Parties

Section 49(a) of the New Zealand Public Health and Disability Act 2000 (the Act) requires PHARMAC to consult, when it considers appropriate to do so, on matters that relate to the management of pharmaceutical expenditure with any sections of the public, groups or individuals that, in the view of PHARMAC, may be affected by decisions on those matters.

Accordingly, a consultation letter was circulated on 28 June 2016 to all suppliers and other parties that, in the view of PHARMAC, may be affected by the recommendations contained in this paper This included all suppliers; all parties who have self identified as wishing to receive all consultations.

The consultation letter and all responses received by 15 July 2016 are attached as Appendix 4

Twelve responses were received, three of which were about posaconazole alone and one of which was about raltegravir alone All but the raltegravir response were generally supportive

Summaries of what PHARMAC staff believe are the significant matters raised in these responses are provided below. For the full response, please refer to Appendix 4.

Stakeholder group	Theme	PHARMAC Staff Comment
Dr Ruth Spearing (Canterbury DHB) Dr Tim Prestidge (Auckland DHB) Eamon Duffy (infectious disease pharmacist, Auckland DHB)	Supportive of funding of posaconazole modified-release tablets Dr Prestidge notes that The current liquid form is very difficult for children to manage three times a day with a high fat meal remembering that the children needing this are often very sick to begin with Therefore there is considerable risk with the current liquid that adherence is poor.	Noted
Pharmacy Guild	Supports the proposal to fund pembrolizumab and posaconazole and to amend the contractual terms of listing of posaconazole oral liquid and raltegravir. Notes the proposed prices for posaconazole modified release tablets and raltegravir. Notes that the usual dose for posaconazole tablets is 300 mg twice daily for one day, followed by 300 mg once daily thereafter For an initial one month treatment a patient would require 93 tablets 100 mg tablets, which is not a multiple of the pack size. Notes that raltegravir is often dispensed for a period less than a whole pack. Notes the financial risk for pharmacies and considers that pharmacies should be able to claim wastage for both of these medicines.	Noted PHARMAC staff note that posaconazole oral liquid does not currently have the wastage rule applied to it, however it does have the OP rule applied which means a multiple of a whole bottle is subsidised for each dispensing We understand that the potential for wastage of the liquid is minimised by clinicians and this is in part enabled by there being one week supply available per bottle. Posaconazole modified release tablets come in packs of 24 tablets. This equates to 7 days of initial treatment with 8 days of treatment ongoing. We anticipate that clinicians would similarly manage the wastage of this product by prescribing to the original pack size rather than an amount of tablets that does not equal a full pack and that this would be supported by the duration of treatment provided by the bottle. With respect to raltegravir, PHARMAC staff note that this is not a new listing and raltegrevir does not currently have wastage applied Raltegrevir is used to treat a chronic condition and we consider that it is unnecessary to apply the wastage rule to this product whereby ongoing chronic treatment is expected

Stakeholder group	Theme	PHARMAC Staff Comment
Federation of Women's Health Councils Aotearoa	Notes concerns about: • the lobbying that prevailed around the pembrolizumab funding discussions. • the incompleteness of the data supporting pembrolizumab and the precedent that PHARMAC would set by funding a treatment still in the development stage • the poor efficacy and side effect profile of pembrolizumab and the lack of long-term safety data • the ongoing funding of dacarbazine given its lack of effectiveness. • the focus on funding of treatment for melanoma rather than funding for prevention (eg sunsmart programmes), given that even newer treatments are not very effective. However, on the assumption that pembrolizumab is funded, supports the proposals to amend the nivolumab access criteria and to establish PD-1 inhibitors as a therapeutic subgroup.	We note that while the evidence for pembrolizumab is not as strong as for nivolumab, our advice is that the two treatments can be expected to provide the same or similar therapeutic effect. Further, both treatments offer significant benefit over the currently available treatment, dacarbazine We note that the proposal to fund pembrolizumab could be expected to provide similar clinical benefit to the status quo situation of nivolumab, Withheld under section Withheld under section 9(2)(b)(ii), 9(2)(ba)(i) and 9(2)(j) Withheld under With respect to dacarbazine, our understanding is that it is only used very infrequently in New Zealand for melanoma, and we understand that it has a range of uses aside from treating malignant melanoma In our view there would be little financial benefit from delisting it and delisting it would raise the risk of health losses by it no longer being available for other conditions. We note that PHARMAC is only responsible for managing pharmaceutical funding so has no control over the funding of prevention programmes referred to in the response.

Stakeholder group	Theme	PHARMAC Staff Comment
Melanoma New Zealand	Supportive of the funding of pembrolizumab, and to allow switching between PD-1 inhibitors on early toxicity Notes that pembrolizumab is considered by clinicians to be equally as effective as nivolumab. Notes the potential for patient confusion as to why one treatment is chosen over the other, noting that service provision resources would likely dictate choice Notes concerns about timely access being inhibited by resource constraints Requests that consideration is given to funding for a BRAF and MEK inhibitor for melanoma patients.	Noted. PHARMAC has received funding applications for BRAF and MEK inhibitor treatments which are under assessment.
Infection Services team at CCDHB	Supportive of the continued funding and access to raltegravir Notes concerns that the proposed contractual extension for raltegravir could defer or delay possible funding of once daily integrase strand transfer inhibitors,	The contractual terms that have been negotiated with MSD for raltegravir would not restrict or inhibit PHARMAC's ability to list further integrase strand transfer inhibitors.

Stakeholder group	Theme	PHARMAC Staff Comment
Cancer Society	Supportive of the funding of a PD1 inhibitor for patients with advanced melanoma.	Noted.
	Notes confusion caused by previous PHARMAC public statements about the nivolumab evidence (greater certainty and better quality evidence than pembrolizumab) and the current position that the two treatments can be considered to have similar efficacy. Notes that the advice that the Cancer Society has had from several experts is that they are the same	We note that while this may have caused some confusion for some parties, the change in view reflects changing information over time, with newer information from PTAC, CaTSoP and clinician feedback all now supporting the view that the two treatments can be considered similarly effective This information was not available when PHARMAC made its earlier statements
	Notes that the pembrolizumab infusion schedule would be more convenient for patients as it would mean less travel.	Noted
	Notes concerns regarding PHARMAC's transparency, assessment and decision-making processes	Noted
	Considers that temporary funding should be made available while evaluation is undertaken for conditions with a high unmet health need and no effective funded treatment options Proposes introduction of an Early Access Scheme.	Noted.

Stakeholder group	Theme	PHARMAC Staff Comment
New Zealand Medical Association	Generally supportive of the proposal in its entirety with some concerns noted.	Noted.
	While it does not oppose the proposal to list pembrolizumab for advanced melanoma, it is of the view that switching from one agent to another in the event of intolerance seems unlikely to happen. It understands that the major forms of intolerance with these agents relate to auto-immune response and that this reaction is likely to be common to both agents.	Noted If the proposal is approved we intend to closely monitor any switching that occurs and would seek feedback from oncologists at a later date about this.
	Supports the establishment of a therapeutic subgroup for PD-1 inhibitors as this may facilitate improved price competition in the future via reference pricing mechanisms	Noted.
	Remains concerned about the additional resource implications for DHBs from listing PD-1 inhibitors.	This point has previously been addressed when the decision was made to fund nivolumab. We note the funding pembrolizumab would reduce the impact on DHB infusion resources compared with the status quo of nivolumab funding
	Notes long-term survival data is unclear and suggests implementation for a limited time period with subsequent review of the evidence.	As with all pharmaceuticals, PHARMAC will continue to monitor new information for this class of treatments as it becomes available
Ministry of Health	Notes that no technical or resource implications are anticipated as a result of the proposal.	Noted

Stakeholder group	Theme	PHARMAC Staff Comment
MelNet (the Melanoma Network of New Zealand Inc)	Supportive of the proposal to fund pembrolizumab, noting the short timeframe may be challenging for DHB resources Considers a robust database is needed to adequately monitor and collect data regarding the introduction of nivolumab and pembrolizumab and offers assistance with respect to this. Does not hold a firm view on the proposal to amend the Special Authority criteria applying to nivolumab Is generally supportive of PD-1 inhibitors being recognised as a therapeutic sub group	Noted.
Dr Kevin Snee, Chief Executive Office, Hawke's Bay DHB	Generally supportive of the proposal as it relates to pembrolizumab and nivolumab (no feedback is provided on the other components). Concerned that the proposal does not fully account for accumulation of patients in the out years. Provides detailed information about the impact of funding nivolumab on Hawke's Bay DHB clinical services and notes concerns about its ability to deliver the additional service within the current funding environment. Notes that funding pembrolizumab would ease some pressure on infusion services but would have no impact on other services (pharmacy, medical oncology, radiology, laboratory).	Noted. The impact on DHB services was assessed as part of the decision to fund nivolumab. We consider that the proposal to fund pembrolizumab would have only a positive impact on DHB services, compared with the status quo of nivolumab funding, although this would related only to infusions as noted by the responder

Legal Advice

Where necessary, management will obtain legal advice on issues such as whether any proposal is consistent with PHARMAC's legislative and public law obligations, including those which may have specific relevance to the particular proposal eg human rights implications of a proposal If the Board considers that further legal advice is required on any issue, this should be communicated to management in advance of the Board meeting. Management will then obtain the required advice.

Legal Advisors' View

Specific legal advice has not been sought on this proposal

Implementation

Section 49(b) of the Act requires PHARMAC to take measures to inform the public, groups and individuals of PHARMAC's decisions concerning the pharmaceutical schedule Accordingly, if the Board adopts the recommendations contained in this paper PHARMAC staff will take the following measures to inform the public, groups and individuals of that decision:

- Notification letter to all suppliers and other parties that may be affected by the recommendations contained in this paper, including DHB CEOs, Funding and Planning Managers, Cancer Service Managers and Hospital Pharmacists
- Notify PTAC, relevant PTAC Subcommittees and other interested parties including consultation responders
- Notify the market through the Pharmaceutical Schedule Update including News story
- Media release

Note that PHARMAC hosted a workshop with DHB cancer centre staff (medical oncologists, pharmacy, nurses, service managers) during the consultation period for this proposal, to discuss issues related to the impact on DHB services of nivolumab funding The impact of the proposed funding of pembrolizumab was also discussed The workshop aimed to help address issues and assist cancer centres with their service impact assessments.

Appendices

Appendix 1 Provisional agreement with MSD

Appendix 2. PTAC and CaTSoP minutes for pembrolizumab.

Appendix 3. Nivolumab patient estimates.

Appendix 4. Consultation letter and responses

MINUTES OF THE PHARMACEUTICAL MANAGEMENT AGENCY (PHARMAC)

BOARD MEETING, 29 JULY 2016

The meeting was held at Level 9, 40 Mercer Street, Wellington, starting at 9:00am with the following attendees:

Present

David Kerr	Acting Chairman, Board Member
Jens Mueller	Board Member
Jan White	Board Member
Nicole Anderson	Board Member
Mark Weatherall	Observer, PTAC Chair
Nigel Murray	Observer, DHB

In attendance

Sarah Fitt	Acting Chief Executive
Andrew Davies	Acting Director of Operations
Peter Alsop	Director of Engagement & Implementation
Jude Urlich	Director of Strategic Initiatives
Mark Woodard	Director of Corporate Services/CFO
John Wyeth	Medical Director
Lizzy Cohen	Board Secretary

Greg Williams, Geraldine MacGibbon, Joy Hu, Simon England, Alan Woods, Janet Mackay, Atene Andrews (PHARMAC staff) attended for relevant items.

1. Directors' Only Discussion

2. Apologies

Stuart McLauchlan, Chair
Steffan Crausaz, Chief Executive
David Lui, Observer, CAC Chair

3. Minutes of Previous Meeting

resolved to adopt the minutes of the meeting on 1 July as being a true and correct record.

David Kerr and Jens Mueller **(carried)**

4. Interests Register

noted the Interest Register.

5. Matters Arising

noted the Matters Arising.

6. Chairman's Report

6.1 Verbal Report

noted the Chairman's verbal report.

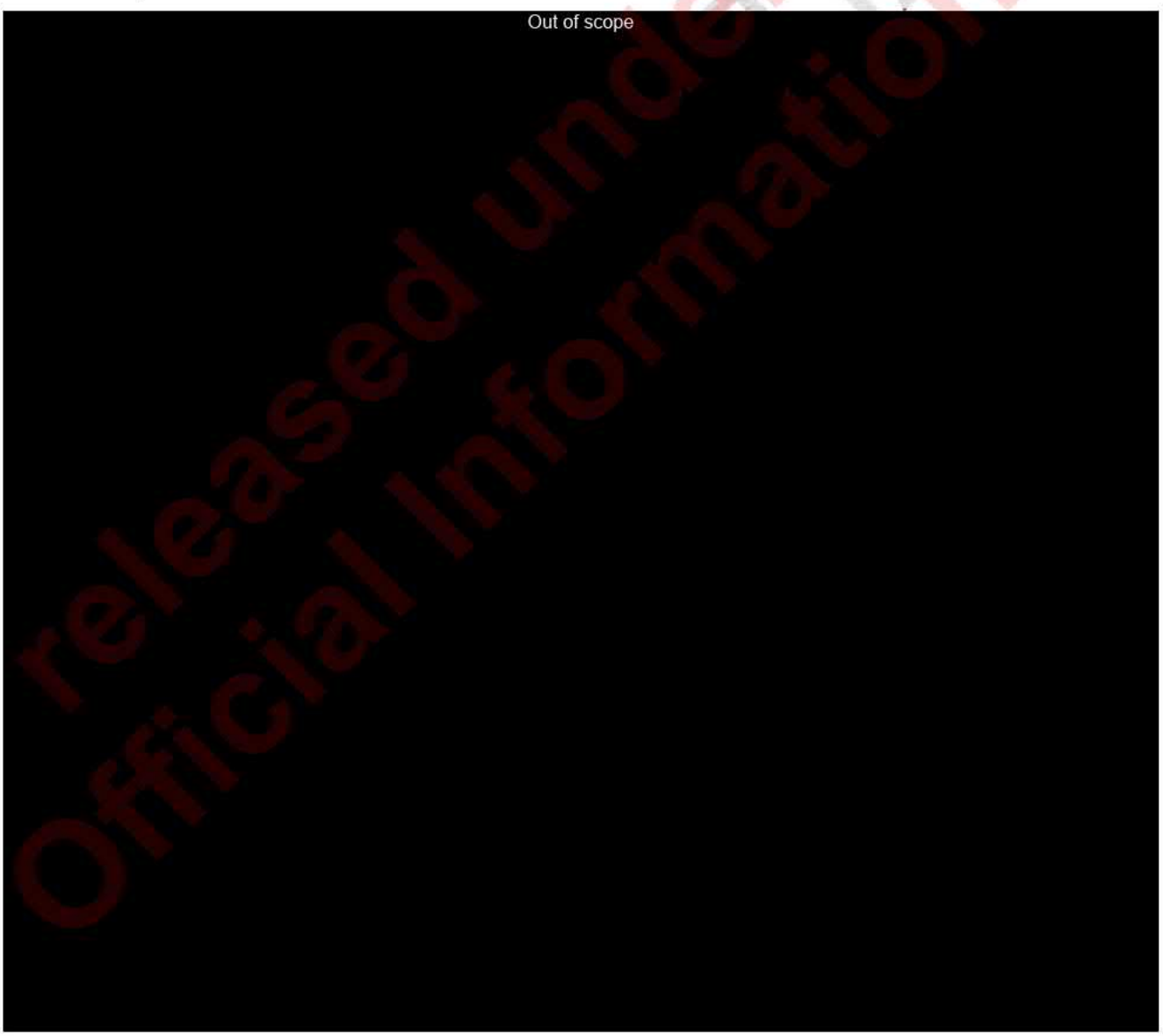
6.2 Correspondence

noted the correspondence received this month.

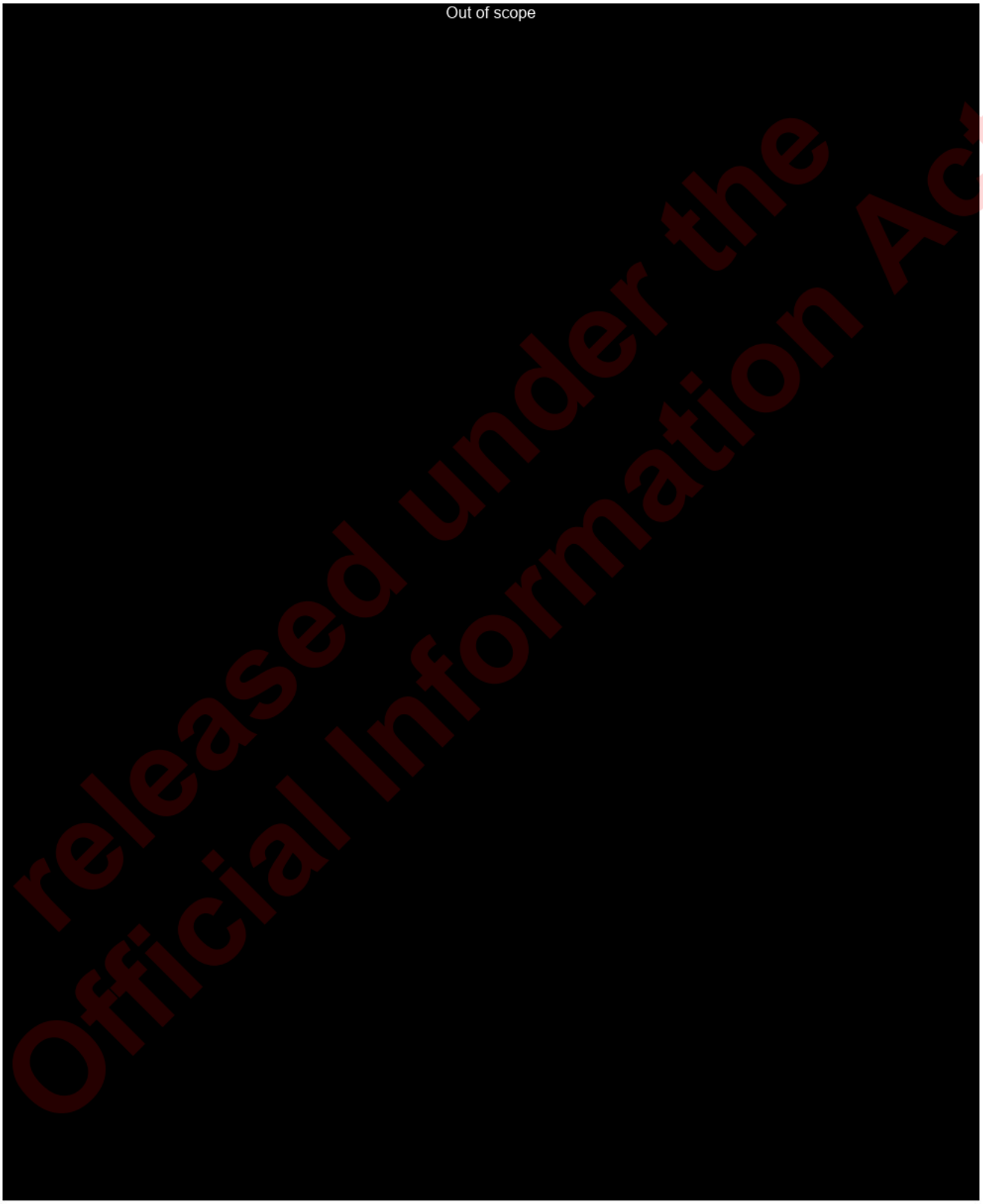
7. Chief Executives Report

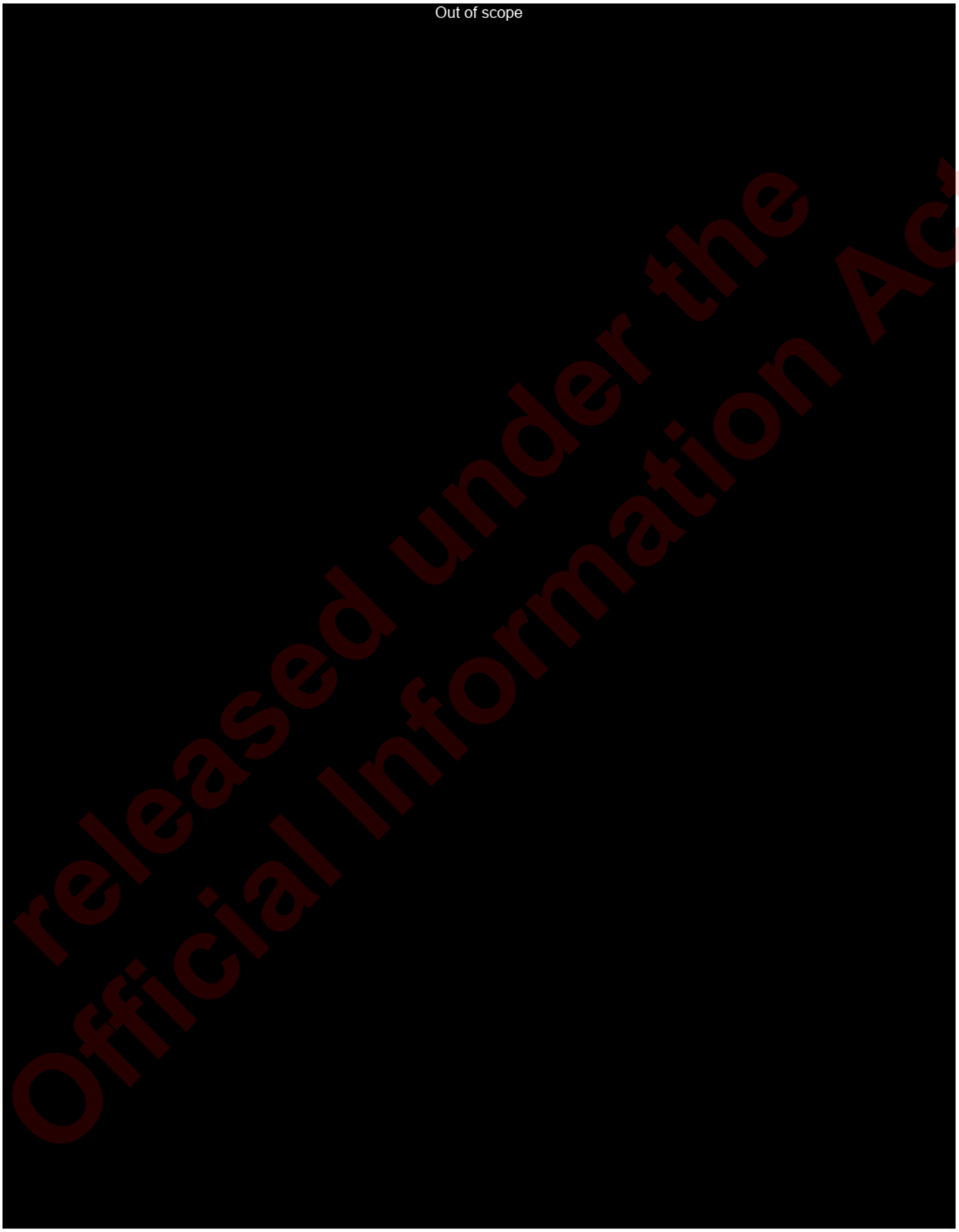
noted the Chief Executive's Report.

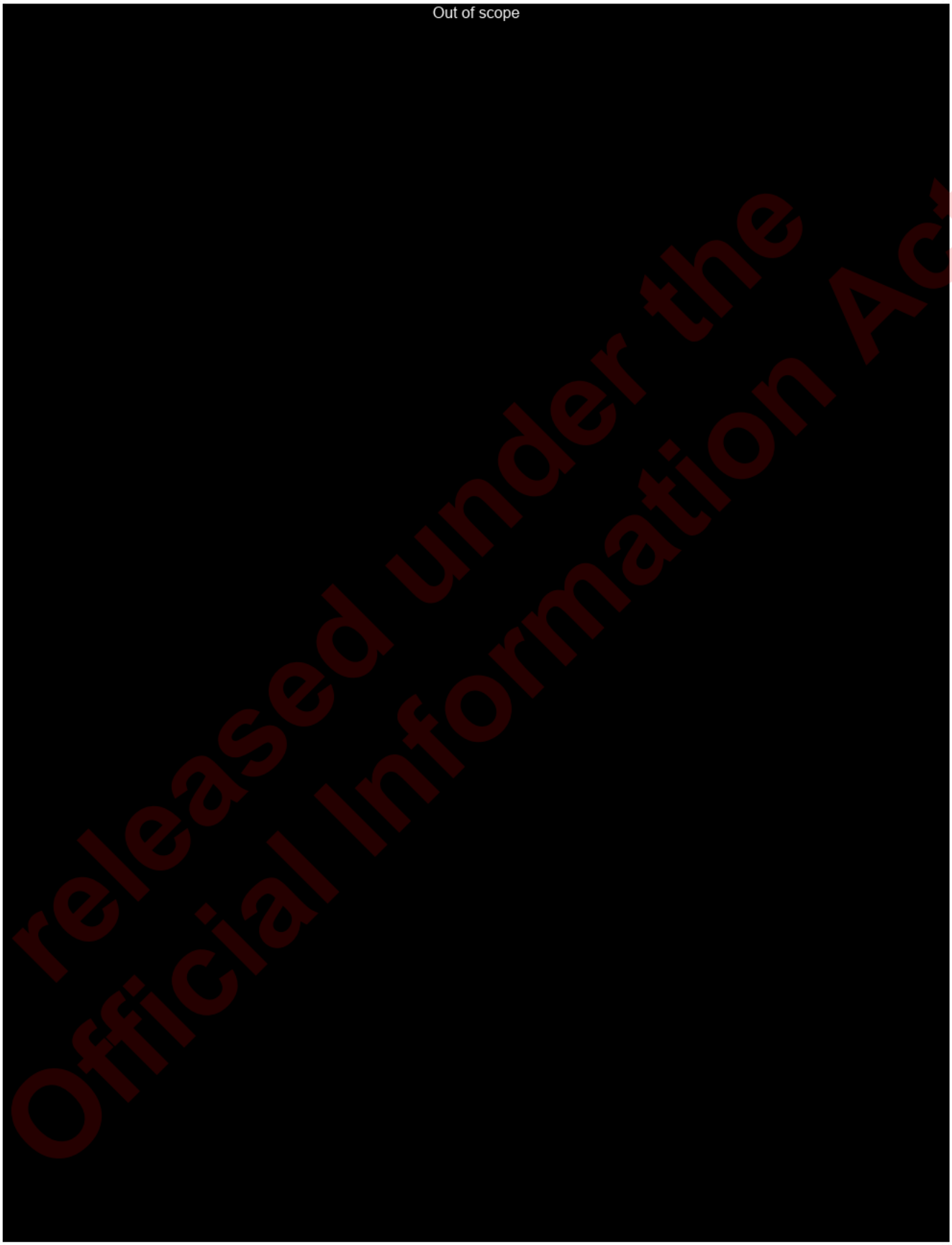
8. Key Issues



9. Schedule and Funding







9.5 Proposal for pembrolizumab, posaconazole and raltegravir

resolved to create a new Therapeutic Group (TG) 3 subheading "Programmed Cell Death-1 (PD-1) Inhibitors" under the Immunosuppressants TG2 subheading in the Oncology and Immunosuppressants therapeutic group in Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 September 2016;

resolved to move the current listing of nivolumab (Opdivo) from the "Monoclonal Antibodies" to the "Programmed Cell Death-1 (PD-1) Inhibitors" TG3 subheading in Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 September 2016;

resolved to list pembrolizumab (Keytruda) under the "Programmed Cell Death-1 (PD-1) Inhibitors" subheading in Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 September 2016 as follows (prices and subsidies expressed ex-manufacturer, excluding GST):

Chemical	Brand	Presentation	Pack size	Price and subsidy
Pembrolizumab	Keytruda	Inj 50 mg vial	1	$2,340.00
Pembrolizumab	Baxter	Inj 1 mg for ECP	1 mg	$49.14

resolved to list pembrolizumab (Keytruda) in Section B of the Pharmaceutical Schedule subject to the following restrictions from 1 September 2016:

PCT only – Specialist

Special Authority for Subsidy
Initial Application — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1 Patient has metastatic or unresectable melanoma stage III or IV; and
2 Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and
3 Either:
3.1 Patient has not received funded nivolumab; or

3.2 Both:
- 3.2.1 Patient has received an initial Special Authority approval for nivolumab and has discontinued nivolumab within 12 weeks of starting treatment due to intolerance; and
- 3.2.2 The cancer did not progress while the patient was on nivolumab; and

4 Pembrolizumab is to be used at a maximum dose of 2 mg/kg every 3 weeks for a maximum of 12 weeks (4 cycles); and
5 Baseline measurement of overall tumour burden is documented (see Note); and
6 Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of pembrolizumab will not be continued beyond 12 weeks (4 cycles) if their disease progresses during this time.

Renewal — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1 Any of the following:
- 1.1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
- 1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
- 1.3 Patient has stable disease according to RECIST criteria (see Note); and

2 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3 No evidence of progressive disease according to RECIST criteria (see Note); and
4 The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
5 Pembrolizumab is to be used at a maximum dose of 2 mg/kg every 3 weeks for a maximum of 12 weeks (4 cycles).

Notes:
Disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47). Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements. Target lesion measurements should be assessed using CT or MRI imaging with the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

- Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

resolved to list pembrolizumab (Keytruda) in Part II of Section H of the Pharmaceutical Schedule subject to the following restrictions from 1 September 2016:

Restricted
Initiation
Medical oncologist
Re-assessment required after 4 months
All of the following:
1 Patient has metastatic or unresectable melanoma stage III or IV; and

2 Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and
3 Either:
    3.1 Patient has not received funded nivolumab; or
    3.2 Both:
        3.2.1 Patient has received an initial Special Authority approval for nivolumab and has discontinued nivolumab within 12 weeks of starting treatment due to intolerance; and
        3.2.2 The cancer did not progress while the patient was on nivolumab; and
4 Pembrolizumab is to be used at a maximum dose of 2 mg/kg every 3 weeks for a maximum of 12 weeks (4 cycles); and
5 Baseline measurement of overall tumour burden is documented (see Note); and
6 Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of pembrolizumab will not be continued beyond 12 weeks (4 cycles) if their disease progresses during this time.

Continuation
Medical oncologist
Re-assessment required after 4 months
All of the following:
1 Any of the following:
    1.1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
    1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
    1.3 Patient has stable disease according to RECIST criteria (see Note); and
2 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3 No evidence of progressive disease according to RECIST criteria (see Note); and
4 The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
5 Pembrolizumab is to be used at a maximum dose of 2 mg/kg every 3 weeks for a maximum of 12 weeks (4 cycles).

Notes:
Disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47). Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements. Target lesion measurements should be assessed using CT or MRI imaging with the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

- Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

resolved to amend the Special Authority restrictions applying to nivolumab (Opdivo) in Section B of the Pharmaceutical Schedule from 1 September 2016 as follows (additions in bold):

Special Authority for Subsidy
Initial Application — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1 Patient has metastatic or unresectable melanoma stage III or IV; and
2 Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and
3 **Either:**
  3.1 Patient has not received funded pembrolizumab; or
  3.2 Both:
    3.2.1 Patient has received an initial Special Authority approval for pembrolizumab and has discontinued pembrolizumab within 12 weeks of starting treatment due to intolerance; and
    3.2.2 The cancer did not progress while the patient was on pembrolizumab; and
4 Nivolumab is to be used at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 12 weeks (6 cycles); and
5 Baseline measurement of overall tumour burden is documented (see Note); and
6 Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of nivolumab will not be continued beyond 12 weeks **(6 cycles)** if their disease progresses during this time.

Renewal application — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1 Any of the following:
  1.1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
  1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
  1.3 Patient has stable disease according to RECIST criteria (see Note); and
2 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3 No evidence of progressive disease according to RECIST criteria (see Note); and
4 The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
5 Nivolumab will be used at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 12 weeks (6 cycles).

Notes:
Disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47). Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements. Target lesion measurements should be assessed using CT or MRI imaging with the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

- Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest

on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

- Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

resolved to amend the restrictions applying to nivolumab (Opdivo) in Part II of Section H of the Pharmaceutical Schedule from 1 September 2016 as follows (additions in bold):

Restricted
Initiation
Medical oncologist
Re-assessment required after 4 months
All of the following:

1 Patient has metastatic or unresectable melanoma stage III or IV; and
2 Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and
3 Either:
3.1 Patient has not received funded pembrolizumab; or
3.2 Both:
3.2.1 Patient has received an initial Special Authority approval for pembrolizumab and has discontinued pembrolizumab within 12 weeks of starting treatment due to intolerance; and
3.2.2 The cancer did not progress while the patient was on pembrolizumab; and
4 Nivolumab is to be used at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 12 weeks (6 cycles); and
5 Baseline measurement of overall tumour burden is documented (see Note); and
6 Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of nivolumab will not be continued beyond 12 weeks **(6 cycles)** if their disease progresses during this time.

Continuation
Medical oncologist
Re-assessment required after 4 months
All of the following:

1 Any of the following:
1.1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
1.3 Patient has stable disease according to RECIST criteria (see Note); and
2 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3 No evidence of progressive disease according to RECIST criteria (see Note); and
4 The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
5 Nivolumab will be used at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 12 weeks (6 cycles).

Notes:
Disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47). Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements. Target lesion measurements should be assessed using CT or MRI imaging with the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

- Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

resolved to establish "Programmed cell death-1 (PD-1) inhibitors" as a therapeutic sub-group from 1 September 2016 in accordance with section 3.3 of PHARMAC's Operating Policies and Procedures, on the basis that, from the advice we have received, PD-1 inhibitors could be expected to produce the same or similar therapeutic effect;

resolved to list posaconazole tablets modified-release 100 mg (Noxafil) in Section B and Part II of Section H of the Pharmaceutical from 1 September 2016 at a price and subsidy of $869.86 per pack of 24 tablets (ex-manufacturer, excluding GST);

resolved to list posaconazole tablets modified-release 100 mg in Section B and Part II of Section H of the Pharmaceutical Schedule subject to the same Special Authority criteria and hospital restrictions (respectively) that apply to posaconazole oral liquid 40 mg per ml at 1 September 2016;

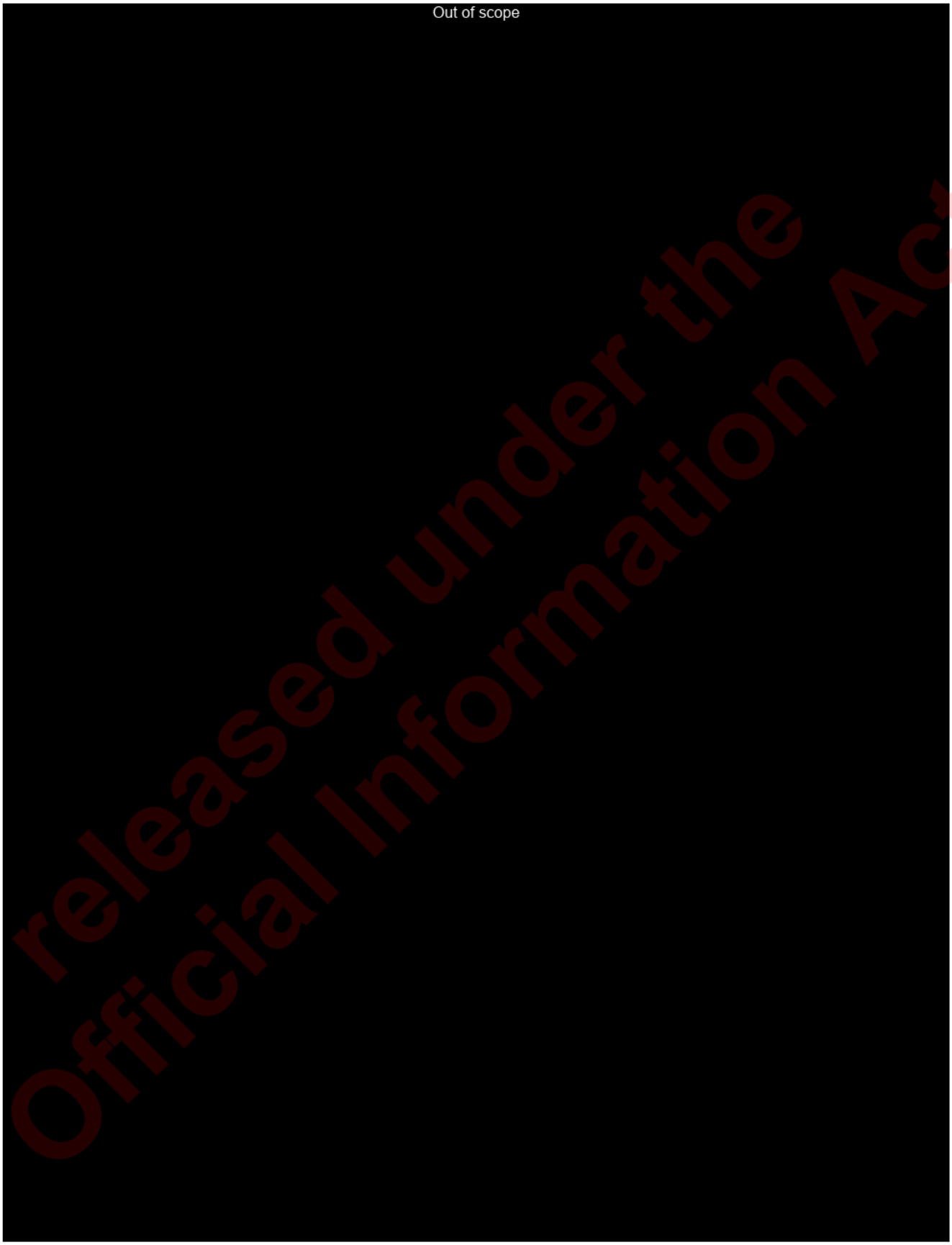
resolved to approve the 22 June 2016 agreement with Merck Sharp and Dohme (New Zealand) Limited;

noted that the above agreement also includes a change in contractual terms for raltegravir 400 mg tablets (Isentress) without any changes to the current Pharmaceutical Schedule listing of this product;

resolved that the consultation on this proposal was appropriate, and no further consultation is required.

David Kerr and Nicole Anderson **(carried)**

Out of scope



Out of scope

[redacted]

The meeting closed at 12.25pm

Chairman

26/8/2016

Date