Methodology and source materials for analysis of Pharmac decision-making

As part of the Pharmac Review

Sapere Research Group

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1. Analysis of decision-making

The decisions Pharmac must make around funding pharmaceuticals have clear impacts on individuals, family, whānau, wider society, and the health system. Pharmac's legislatively fixed budget means there are always trade-offs to be made across illnesses and pharmaceuticals available. The New Zealand public and Government therefore expect Pharmac to employ a rigorous, transparent, and consistent process that explains why a decision was made, showcasing how the decision was arrived at.

Decision-making was called upon as an area of scrutiny in the wider review of Pharmac. Analysis of some select investment decisions made by Pharmac provided insight into whether Pharmac's decision-making (and the analysis conducted to inform decisions) is rigorous, transparent, consistent, and delivers the outcomes New Zealanders expect.

1.1 Purpose and context of this work

The purpose of undertaking analysis of Pharmac's decision-making was to form a holistic view of Pharmac's capacity and capability in the roles of assessing and procuring pharmaceuticals for New Zealand.

Sapere was commissioned by the Pharmac Review Panel in a supporting role for its analytical capabilities. Decision-making analysis was one of a few roles Sapere has served throughout the review. This analysis was also supported by Melissa McLeod and Ricci Harris, two public health academics with the expertise to critically assess cost-effectiveness and disease modelling assumptions and robustness.

As per the scope of the work, Sapere looked to employ a methodology that assessed the analytical capability and robustness of Pharmac decision-making, as well as the consideration of equity within its analysis.

1.2 Methodology

There are two components to the analysis of decision-making. This report covers what Sapere has done (i.e. one of the two components); however, it may reference the work Melissa McLeod and Ricci Harris have done since the two components form the wider assessment of decision-making.[1] There may also be crossover in the analysis due to the same issues appearing in different places throughout Pharmac documentation.

The Pharmac Review Panel chose to analyse case studies of six different investment decisions (five unique pharmaceuticals). The case study approach was selected to allow for targeted, in-depth analysis given time and budget constraints. The purpose of analysing these case studies was to form a view on the:

[1] McLeod M, Harris R. Review of Pharmac cost-utility analysis modelling approaches in relation to Māori health inequity. Pharmac Review, Wellington 2021.

- strength of Pharmac's capability to undertake technical analysis
- robustness of Pharmac's decision-making
- consideration of equity within Pharmac's analysis, given Pharmac's responsibilities as a public health entity and Te Tiriti partner.

The table below outlines the pharmaceuticals that were chosen by the review to be used as case studies.

Table 1: Pharmaceuticals assessed within the case studies

Pharmaceutical	Disease
Ustekinumab, a monoclonal antibody medication	For treatment of Crohn's disease, a chronic inflammatory bowel disease that affects the lining of the digestive tract
Nusinersen, in a class of medications called antisense oligonucleotide inhibitors	A novel treatment for spinal muscular atrophy, a rare neuromuscular disorder
Pembrolizumab, a humanized antibody used in cancer immunotherapy	As an alternative treatment for non-small cell lung cancer
Pembrolizumab	An additional treatment for metastatic and unresectable melanoma
Empagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor	A treatment to help reduce the risk of cardiovascular and renal complications in people with type 2 diabetes
Venlafaxine, an antidepressant medication of the serotonin-norepinephrine reuptake inhibitor class [brand switch]	Used to treat major depressive disorder, generalized anxiety disorder, panic disorder, and social phobia. It may also be used for chronic pain.

Sapere received internal documentation for each of the pharmaceuticals, showing what information/data and assumptions were used in coming to a decision, as well as other factors were taken into consideration.

These case studies were chosen by the panel for a few reasons. Firstly, these cases are significant in the context of New Zealand, particularly for sub-groups of the population such as Māori, Pasifika, and the disabled community because of disease prevalence, access, and potential for benefit. Secondly, these medicines have been at the centre of public discourse for a long period of time given overseas availability and experiences.

This selection of cases was expected to provide the broadest insight into the decision-making process and allow for the greatest generalisability given the time and budget constraints of the review.

Melissa McLeod and Ricci Harris drilled into the cost-utility analysis and disease modelling performed by Pharmac to assess its rigour and robustness, alongside its assumptions and considerations. A key focus here was the extent to which Pharmac incorporated equity into the technical analysis and used appropriate information for a New Zealand context.

Sapere conducted an "audit" for each of the case studies of the Pharmac analytical process and documentation against the following internal guidance documents Pharmac provided:

- The *Prescription for Pharmacoeconomic Analysis (PFPA)*, which details the methodological and technical recommendations for undertaking cost-utility analysis.
- *Factors for Consideration (FFC) Internal Guidance*, which shows how and where the FFC input into decisions made.

Sapere chose 15 criteria from the *PFPA* to assess the case studies against, and 16 criteria to assess the case studies against from the *FFC Internal Guidance*. These criteria and Sapere's assessment rationale can be seen in an attached appendix. Each criteria received a ranking between 0 and 3. The meanings of each score are as follows:

- **0 = adequate**; the analysis meets the guidance and/or expectation.
- **1 = slight deviation from guidance**; however, it is unlikely to have made a difference to the decision.
- **2 = deviation that should be recorded**; it may also be material and could have had an impact on the decision.
- **3** = **material and significant deviation**; likely had a noticeable impact on the decision.

It is possible there is some cross-over between the "audit" of *PFPA* and *FFC Internal Guidance* criteria and therefore analysis due to the way the documents are written and their interdependence in decision-making.

It is important to note that both internal guidance documents are not as prescriptive as the name(s) might suggest. Pharmac hold the right to deviate from guidance where it sees necessary. Employing an "audit" style approach allowed Sapere to see where Pharmac has deviated from internal guidance recommendations, and given Pharmac's discretion to deviate from guidance, whether deviations are justified and considered appropriate.

The combination of the "audit" style approach as well as the technical analysis of cost-utility and disease modelling provides a good picture of what Pharmac has done and whether it aligns with what New Zealanders would ultimately expect from Pharmac.

1.3 Documents received

Sapere received numerous documents across the six case studies. These included:

- decision models (disease analysis, cost-utility analysis)
- specialist advisory committee papers
- hot-topic, pre-prioritisation, and prioritisation meeting notes as well as minutes
- in one instance, the pharmaceutical company application.

The table below lists the documents received for each medicine.

Table 2: Documents received from Pharmac for each of the case study medicines

Empagliflozin	• PTAC paper • PTAC correspondence • Diabetes subcommittee discussion • 2 hot topic meeting papers • 2 hot topic meeting minutes • Pre-prioritisation meeting presentation • Pre-prioritisation meeting minutes • TAR • Prioritisation dossier • Prioritisation meeting minutes • Clinical advice from subcommittee • Diabetes RFP and combined consultation responses • Decision tree model
Nusinersen	• Supplier proposal • Rare disorder subcommittee paper • Resubmission • Rare disorder subcommittee resubmission paper • Supplier proposal (2nd) • Supplier proposal (3rd) • CUA and BIA • PTAC paper • TAR • Prioritisation minutes • Supplier proposal (4th) • Prioritisation dossier • Supplier proposal (5th) • Supplier proposal (6th)

	• Proposal correspondence from Pharmac • Supplier proposal (7th)
Venlafaxine	• Board paper • Board paper appendices
Pembrolizumab (lung cancer)	• PTAC paper • CaTSoP paper • PTAC paper (2nd) • PTAC correspondence • Hot topic presentation • CaTSoP review • CaTSoP paper (2nd) • CaTSoP paper (3rd) • Hot topic presentation (2nd) • Hot topic minutes • Pre-prioritisation paper • Decision models • Pre-prioritisation paper (2nd) • Pre-prioritisation minutes • Prioritisation dossier • Prioritisation meeting minutes • TAR
Pembrolizumab (melanoma)	• CaTSoP paper • PTAC paper • Pre-prioritisation slides • Prioritisation dossier • Prioritisation meeting minutes • TARs (2)

	• PTAC paper (2nd) • CaTSoP paper (2nd) • Decision paper • Decision model
Ustekinumab	• PTAC paper • Hot topic paper • Hot topic minutes • Pre-prioritisation paper • Pre-prioritisation minutes • Pre-prioritisation minutes (2nd) • Prioritisation meeting minutes • Hot topic paper (2nd) • Hot topic minutes (2nd) • Hot topic paper (3rd) • Prioritisation dossier • Prioritisation dossier (2nd) • TAR • Prioritisation meeting minutes (2nd) • Decision model

1.4 Analysis of decision-making against criteria

The matrices below show our analysis of decision-making against the specified criteria for both the *PFPA* and the *FFC Internal Guidance* document, as well as the scores applied. Justifications for scoring are provided alongside each of the criteria.

Comparison of empagliflozin against the Pharmac PFPA

Effectively, this acts as an audit of the different medicines against the Pharmac PFPA to assess deviations from recommended methodology. It also allows us to rank from 0 - 3 on a scale of severity of "error" (0 where it is adequate, 1 being a deviation but not likely to have made a difference to the decision, 2 being a deviation that should be noted and may be material, and 3 being a deviation that is material and significant).

Section #	Section header	General description	Empagliflozin	Score	Comments
3.1	Models	Models should avoid unnecessary complexity and should be transparent, well described, and reproducible.	The CUA models did not account for health equity in their structure, data inputs or outputs. This model does not provide an assessment of the likely cost-effectiveness of empagliflozin in New Zealand, but is instead an assessment of the NZ-based costs of the health gains achieved for the RCT population. This important difference was unclear until we opened the model. PHARMAC therefore need to be more explicit in their documentation where their CUAs are not assessing a medicine for the New Zealand healthcare context or population and provide greater critique of the relevance of their data inputs in the New Zealand context, including for Māori.	2	Issues with model appropriateness.
3.1.1	Model transparency	Model inputs and assumptions need to be clearly stated and the rationale for the inputs and assumptions documented and explained.	The models do not account for any potential differences by age, gender or ethnicity. The RCT outcomes included in the model are the rates of all-cause mortality and heart failure hospitalisations. These outcomes differ to the primary outcome of the RCT which was a composite measure of cardiovascular outcomes (including cardiovascular mortality, non-fatal MI and non-fatal stroke). The RCT stratified the primary (cardiovascular) outcome measure by demographic and clinical variables revealing a lack of treatment effect for those aged under 65 years, of 'black' race (although underpowered), for those with glycated HbA1c of greater than 8.5%, and for those with a BMI over 30 (Zinman et al. 2015). Similar stratification was performed for cardiovascular deaths alone, with protective effect of empagliflozin across all examined strata. Within the RCT papers there was no stratification of the outcomes that were used in the PHARMAC model, and no discussion about the validity of the implicit assumption made in the PHARMAC model that the impact of empagliflozin on all-cause mortality and heart failure hospitalisations does not vary by age, gender, race/ethnicity or baseline health measures. In the PHARMAC model, data on the baseline proportions in the model health states (e.g. combinations of those on insulin, with macro albuminuria, and on dialysis), and progressions across these states (to macro albuminuria and renal dialysis) were drawn from the RCT rather than NZ data. Similarly, the PHARMAC model uses RCT data on the overall rates of all-cause mortality and heart failure hospitalisations. Despite an acknowledgement in the TAR that Māori suffer a higher rate of progression to complications than the total New Zealand population, no further detail was given. Data from the 2013/14 New Zealand Health Survey show that Māori rates of renal failure with concurrent diabetes were more than five times that of non-Māori (RR 5.55, CI 5.07–6.07) (Ministry of Health). Failing to account for the much higher progression to renal failure in Māori will underestimate the health benefits of empagliflozin in preventing renal failure for Māori and the healthcare costs saved as a result of less dialysis.	3	Model does not address population heterogeneity. Use of trial population to generalise to New Zealand public.
3.2	Time horizon and cycle length	The report should always justify the time horizon used in the analysis.	The selection of a 10-year time horizon was based on impacts of aging and other factors. Sensitivity analysis on a 15-year time horizon was undertaken.	0	Meets guidelines.
3.4	Target population	Target population is the NZ population most likely to receive treatment. It may be necessary to use subgroup analyses if treatment can not be targeted to those most likely to benefit… In cases where the subgroup was defined retrospectively in the clinical trial(s), the data should be used cautiously and evidence of statistical heterogeneity reported.	We would expect some discussion of how comparable the trial disease proportions and progressions are with NZ data, and with Māori data specifically. If they were found to differ in important ways from NZ and/or Māori specific data, it would be preferable to instead use NZ data in the model, or alternatively run sensitivity analyses on these important parameters in order to gain an understanding of the degree to which the model outputs may be an under or overestimate. It is possible that such sensitivity analyses were undertaken but have not been released to us. We would argue that they provide critical information and therefore should be a standard part of PHARMAC reporting.	2	Analysis does not reflect the New Zealand target population, no comment on appropriateness.
3.5	Comparator(s)	Comparator(s) used in analyses should be the funded treatment that most prescribers or clinicians would replace in NZ clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace).	Not applicable.	0	No issue.
4.1	Data sources	All appropriate levels of evidence should be identified; however, well-conducted RCTs and meta-analyses are the preferred data sources when estimating relative treatment effects. In the absence of valid RCTs, evidence from the highest available level of study design should be considered with reference to the limitations of the study design.	Not easily visible.	1	Unclear how much effort has gone into seeking relevant, robust information beyond that supplied by the applying company.

4.4	Assessing data quality	Trials should be critically appraised using the GATE framework, with consideration given to the internal and external validity of the trials. Grades of evidence should be assigned, and assessment undertaken on the applicability of the trials to the New Zealand health sector [known biological factors that may alter effect of pharmaceutical, dependency on way of administration, complex procedure, infrastructure required, other factors]. When high-quality studies are available, these should be the preferred data source when estimating relative treatment effects.	It does not appear the trial has been critically appraised using the GATE framework.	2	Unclear whether the GATE framework has been used for analysing the data quality.
5.2	Extrapolation of data	Methodology, limitations, and any possible bias associated with extrapolating data should be clearly described in the report and explored through sensitivity analysis. This includes extrapolating data from clinical trials to the longer term (or to final outcomes), generalising results from clinical trials to the NZ clinical setting by taking into account non-compliance, and undertaking indirect comparisons of trials. It is recommended that in the absence of conclusive data, conservative assumptions be used in the analysis.	The heavy reliance on international RCT data in the CUA creates an issue with generalisability of the CUA findings to the NZ population, and to the Māori population specifically. The model uses population and effectiveness data directly from the EMPAG-REG OUTCOME RCT (Zinman et al. 2015; Wanner et al. 2016) that differ in important ways for New Zealand (see below). For example, the RCT population were drawn from a number of different countries with varying population demographics and healthcare systems, had an average age of 63 years and 71% of participants were male (Zinman et al. 2015). At a minimum we would expect to see some discussion of how generalizable the RCT results (and the CUA) are to the NZ total population with diabetes, and separately to the Māori population with diabetes. We expect that there are large differences between the RCT population and the Māori population, at least with respect to age and access to healthcare impacting on diagnosis of CVD and access to existing diabetes treatments, and likely also important differences between the RCT and the total NZ population (including gender proportions) that are critical to consider in the presentation and interpretation of the modelling results.	3	No comment on the generalisability of the RCT data and the findings from the trial to the New Zealand population and/or clinical setting.
6.1.2	Health benefit to family, whānau, and society	It is recommended that only the HRQOL of the patient being treated should be included in the base-case analysis. If the treatment might have a measurable but indirect impact on the HRQOL of others, such as family and caregivers, this could be estimated and discussed in the report as a scenario.	A limitation of using a funder perspective in modelling is the lack of any consideration of the considerable burden on caregivers/whānau of individuals with diabetes and complications of diabetes, including dialysis. Given inequities in diabetes, these may well have disproportionate impacts for whānau Māori.	1	Not explored.
6.2	Health-related quality of life instruments	The NZ EQ-5D Tariff 2 should be referred to first when measuring HRQOL, and should be used to describe the health states. The Global Burden of Disease disability weights and published literature should be used to check for consistency with the estimated EQ-5D values.	Not used. Pharmac staff considered literature from had derived utilities that were boarder generalisable to NZ.	1	Discussion of how appropriate this is may be beneficial to include.
6.2.2	Obtaining utility values	If subjective judgement is used to map health states, these health states should be validated through either published literature or expert clinical input. The report should provide a detailed description of the health state and the impact on HRQOL.	There was good discussion provided around the process for deciding on a set of utilities and reflection on the range of utility estimates in the literature and sensitivity analyses on utility values.	0	Followed guidance.
7.2	Pharmaceutical costs	Should use net pricing from the pharmaceutical supplier, be based on the dose used in the key clinical trials (unless evidence of efficacy for different doses in clinical practice) and take into account the lower price of a future generic pharmaceutical. Dispensing fees and pharmacy mark-up should be included. The cost of co-administered pharmaceuticals and any significant costs with administering the pharmaceutical should also be taken into account.	Cannot assess this, due to redaction of pricing.	0	Cannot be assessed.
7.8	Indirect patient costs	Should not be included in cost-utility analyses as costs. Reductions in such costs may be included as health benefits.	Not visible.	1	Unclear if these have been explored, even qualitatively.
7.9	Sourcing and reporting of cost data	Only NZ costs should be used in CUAs. The use of cost data from overseas or clinical trials is not recommended. Expert clinical opinion should be sough regarding likely treatment patterns and applicability of resource use.	Costs seem to come from NZ sources (ANZDATA 41st Annual Report, BPAC, etc.).	0	Followed guidance.
10.1	Parameter uncertainty	Sensitivity analysis should include univariate (simple) analysis and multivariate analysis… any uncertainty in the analysis should be fully tested and described in the report.	Model included sensitivity analyses on discount rates, baseline proportions, clinical parameters, utilities, pharmaceutical costs, time horizons, and other costs.	0	Followed guidance.

Comparison of ustekinumab against the Pharmac PFPA

Effectively, this acts as an audit of the different medicines against the Pharmac PFPA to assess deviations from recommended methodology. It also allows us to rank from 0 - 3 on a scale of severity of "error" (0 where it is adequate, 1 being a deviation but not likely to have made a difference to the decision, 2 being a deviation that should be noted and may be material, and 3 being a deviation that is material and significant).

Section #	Section header	General description	Ustekinumab	Score	Comments
3.1	Models	Models should avoid unnecessary complexity and should be transparent, well described, and reproducible.	Overall, the TAR provided a good overview of the model and key assumptions. A major strength of this modelling was the use of the PHARMAC IBD model which included Crohn's disease and Ulcerative colitis, and a few medications.	0	Followed guidance and used the IBD model.
3.1.1	Model transparency	Model inputs and assumptions need to be clearly stated and the rationale for the inputs and assumptions documented and explained.	By using this consistent model structure, there is improved consistency in the modelling of medicines for the treatment of IBD.	0	Followed guidance and used the IBD model.
3.2	Time horizon and cycle length	The report should always justify the time horizon used in the analysis.	20 years, justified based on limited clinical data, and uncertain relapse and remitting natural history of disease.	0	Followed guidance, justifying the time horizon used.
3.4	Target population	Target population is the NZ population most likely to receive treatment. It may be necessary to use subgroup analyses if treatment can not be targeted to those most likely to benefit... In cases where the subgroup was defined retrospectively in the clinical trial(s), the data should be used cautiously and evidence of statistical heterogeneity reported.	New Zealand age-specific mortality rates were used for the background mortality rate in these models. While it may be reasonable not to model a treatment for Crohn's disease specifically for Māori given it is identified as a rare condition (discussed below), there are a number of important equity issues that required further exploration in the TAR and prioritisation dossier. Crohn's disease can be a difficult condition to diagnose, and diagnosis is often delayed (BPAC, 2021). This then raises the question of whether the low incidence of Crohn's in Māori is real, or a result of barriers in access to diagnosis. Further to this, there is no assessment of whether Māori with Crohn's disease are receiving best practice care and have had equitable access to the first- and second-line treatments required in order to then access ustekinumab as a second- or third-line treatment.	2	Exploration of underdiagnosis and existing inequities within Māori access, diagnosis, and treatment would be beneficial.
3.5	Comparator(s)	Comparator(s) used in analyses should be the funded treatment that most prescribers or clinicians would replace in NZ clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace).	Use of placebo.	0	Followed guidance.
4.1	Data sources	All appropriate levels of evidence should be identified; however, well-conducted RCTs and meta-analyses are the preferred data sources when estimating relative treatment effects. In the absence of valid RCTs, evidence from the highest available level of study design should be considered with reference to the limitations of the study design.	Given the lack of New Zealand data on Crohn's it was necessary to use overseas data in the models. Where international data are used it is important to include some discussion of the relevance of these data in the New Zealand context. The ustekinumab modelling assumes an average starting age of 40 years, consistent with the average age of 37-40 years the international clinical trial population (Feagan et al, 2016).	1	Discussion of the relevance of international data to the New Zealand context necessary. Unclear if there was meta-analyses conducted.
4.4	Assessing data quality	Trials should be critically appraised using the GATE framework, with consideration given to the internal and external validity of the trials. Grades of evidence should be assigned, and assessment undertaken on the applicability of the trials to the New Zealand health sector [known biological factors that may alter effect of pharmaceutical, dependency on way of administration, complex procedure, infrastructure required, other factors]. When high-quality studies are available, these should be the preferred data source when estimating relative treatment effects.	Not visible.	1	Unclear whether the GATE framework has been used to assess the trial information used in analysis.
5.2	Extrapolation of data	Methodology, limitations, and any possible bias associated with extrapolating data should be clearly described in the report and explored through sensitivity analysis. This includes extrapolating data from clinical trials to the longer term (or to final outcomes), generalising results from clinical trials to the NZ clinical setting by taking into account non-compliance, and undertaking indirect comparisons of trials. It is recommended that in the absence of conclusive data, conservative assumptions be used in the analysis.	If Māori are known or suspected to be underdiagnosed and undertreated (with existing options), the model should account for this rather than assume ongoing inequities. Within the prioritisation dossier, Crohn's disease is not a "Māori health area of focus". Under "Māori health need", it is noted that Crohn's disease is rare in Māori and Pacific. This statement is based upon data from a study in the Canterbury DHB population in 2006, where 1% (n=8) of recruited Crohn's cases were Māori, and no Pacific Crohn's cases were identified and recruited into the study (Gearry et al. 2006). We note that study age-standardised total population rates are compared with Māori crude rates in the PHARMAC documentation. A more recent study through Otago DHB found similarly low rates of Crohn's disease in Māori (n=4) (Coppell et al. 2018). There are some important limitations to the study's findings that are not identified in the prioritisation dossier. Both Otago and Canterbury DHBs have relatively small proportions of Māori (~7% in both Otago and Canterbury versus 15% nationally), limiting the studies abilities to measure incidence and prevalence in Māori with precision. In both studies, recruitment strategies heavily relied upon existing Crohn's diagnoses and engagement with the health system. In the Otago study, cases were identified through hospital records, and in the Canterbury study recruitment onto the study was through GP and hospital clinics (the former by searching for terms relating to Crohn's and known treatments), Crohn's support groups, and more generally such as through newspaper articles and posters. In addition to a likely underestimate of Crohn's in Māori due to the studies recruitment strategies (healthcare based and selecting for more severe illness), there is a known undercount of Māori in health data (NHI) of around 15-20% (Reid et al. 2016; Cleary 2021), and Māori are likely to be differentially impacted by the difficulties in diagnosing Crohn's disease due to inequities in the healthcare system, particularly in access to primary care.	2	Important considerations to be made and explorations about the prevalence of Crohn's within groups typically experiencing inequities in health outcomes and access to health services.
6.1.2	Health benefit to family, whānau, and society	It is recommended that only the HRQOL of the patient being treated should be included in the base-case analysis. If the treatment might have a measurable but indirect impact on the HRQOL of others, such as family and caregivers, this could be estimated and discussed in the report as a scenario.	No mention of health benefit to family, whānau, and society. Not included as a scenario in the modelling. Unclear to what extent there would be significant impacts for family, whānau, and society.	1	No exploration of potential benefits wider than the patient.

6.2	Health-related quality of life instruments	The NZ EQ-5D Tariff 2 should be referred to first when measuring HRQOL, and should be used to describe the health states. The Global Burden of Disease disability weights and published literature should be used to check for consistency with the estimated EQ-5D values.	Seems to be applied, incorporated into the IBD model.	0	Followed guidance.
6.2.2	Obtaining utility values	If subjective judgement is used to map health states, these health states should be validated through either published literature or expert clinical input. The report should provide a detailed description of the health state and the impact on HRQOL.	There was a good level of discussion provided around the process for deciding on a set of utilities and reflection on the wide range of utility estimates in the literature. The TAR notes that sensitivity analyses were undertaken around the size of the utilities.	0	Followed guidance.
7.2	Pharmaceutical costs	Should use net pricing from the pharmaceutical supplier, be based on the dose used in the key clinical trials (unless evidence of efficacy for different doses in clinical practice) and take into account the lower price of a future generic pharmaceutical. Dispensing fees and pharmacy mark-up should be included. The cost of co-administered pharmaceuticals and any significant costs with administering the pharmaceutical should also be taken into account.	Seems to be captured.	0	Followed guidance.
7.8	Indirect patient costs	Should not be included in cost-utility analyses as costs. Reductions in such costs may be included as health benefits.	Nothing captured as health benefits.	0	Followed guidance.
7.9	Sourcing and reporting of cost data	Only NZ costs should be used in CUAs. The use of cost data from overseas or clinical trials is not recommended. Expert clinical opinion should be sough regarding likely treatment patterns and applicability of resource use.	Health system costs of Crohn's disease primarily came from the PHARMAC cost resource manual. Utilisation of health services drew from a prior assessment of adalimumab for Ulcerative Colitis where utilisation data is stated to have been "provided by the supplier from a small survey of clinicians" (Table 1). It is unclear whether any of these clinicians worked within the New Zealand health system, or if there was any validation of these data for use in the New Zealand setting.	1	Further exploration required of the validity of the cost inputs used.
10.1	Parameter uncertainty	Sensitivity analysis should include univariate (simple) analysis and multivariate analysis… any uncertainty in the analysis should be fully tested and described in the report.	The TAR acknowledges the large uncertainty around the loss of response estimate and appropriately undertook sensitivity analyses to explore this parameter further. Five-year follow-up data have subsequently been published which show that only 41% of participants on 8 weekly ustekinumab continued therapy up to five years with the main reasons being withdrawal of study consent, adverse events and lack of efficacy (Sandborn et al. 2021). A major strength of this modelling was the use of the PHARMAC IBD model which included Crohn's disease and Ulcerative colitis, and a few medications. By using this consistent model structure, there is improved consistency in the modelling of medicines for the treatment of IBD. The model itself included several sensitivity analyses on key parameters where there was a lack of evidence and high uncertainty such as loss of response, utilities and health system costs.	0	Followed guidance.

Comparison of nusinersen against the Pharmac PFPA

Effectively, this acts as an audit of the different medicines against the Pharmac PFPA to assess deviations from recommended methodology. It also allows us to rank from 0 - 3 on a scale of severity of "error" (0 where it is adequate, 1 being a deviation but not likely to have made a difference to the decision, 2 being a deviation that should be noted and may be material, and 3 being a deviation that is material and significant).

Section #	Section header	General description	Nuinersen	Score	Comments
3.1	Models	Models should avoid unnecessary complexity and should be transparent, well described, and reproducible.	Overall the TAR provided a good overview of the model and key assumptions. Models for all types of SMA.	0	Followed guidance.
3.1.1	Model transparency	Model inputs and assumptions need to be clearly stated and the rationale for the inputs and assumptions documented and explained.	The CUA models did not account for health equity in their structure, data inputs or outputs. This is a reasonable approach given that Spinal Muscular Atrophy (SMA) is a rare condition with very few cases diagnosed in Māori, and limited New Zealand data. There was also a good level of discussion around using progression free survival (without loss of motor skills) rather than overall survival from the clinical trials to account for differences in the management of SMA in New Zealand, specifically the lack of ventilation assistance for SMA in New Zealand. Detection of pre-symptomatic SMA was assumed to occur through an additional test being added onto the current newborn heel prick testing. Insufficient consideration was given to the costs of establishing a new screening programme for SMA.	2	Exploration of the feasibility and available capacity required to add screening programme onto existing screening programmes for other conditions. Untested, assumption could lead to unexpected costs and capacity issues.
3.2	Time horizon and cycle length	The report should always justify the time horizon used in the analysis.	A clear rationale was given for a 10-year time horizon for the symptomatic SMA model, referring to the lack of long term data. In contrast no rationale is given for the use of an 80-year time horizon for the pre-symptomatic model which drew on clinical trials of a similar duration to the symptomatic model.	2	Explanation required for the use of an 80-year time horizon in one of the models, and why it is significantly different to the 10-year used in the symptomatic model and trials.
3.4	Target population	Target population is the NZ population most likely to receive treatment. It may be necessary to use subgroup analyses if treatment can not be targeted to those most likely to benefit… In cases where the subgroup was defined retrospectively in the clinical trial(s), the data should be used cautiously and evidence of statistical heterogeneity reported.	Given the lack of New Zealand data on SMA it was necessary to use overseas data in the models. Within the prioritisation dossier, “Māori health areas of focus” and “Māori health need” were noted as “not applicable”.	0	Followed guidance.
3.5	Comparator(s)	Comparator(s) used in analyses should be the funded treatment that most prescribers or clinicians would replace in NZ clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace).	No comparator available in terms of medicine, just current SOC which is physio etc.	0	Followed guidance.
4.1	Data sources	All appropriate levels of evidence should be identified; however, well-conducted RCTs and meta-analyses are the preferred data sources when estimating relative treatment effects. In the absence of valid RCTs, evidence from the highest available level of study design should be considered with reference to the limitations of the study design.	Similarly, there was no discussion on the relevance to New Zealand of using a Swedish SMA Type I-III incidence rate of 8.5 cases per 100,000 live births within the budget impact assessment (Arkblad et al. 2009). Other incidence rates used within the literature and supplier proposal.	2	The implications of using this figure instead of others from literature (or a combinatory method of all) have not been well discussed. As a result of high treatment cost, there may be significant variation in BIA if incidence rates are assumed to be considerably different to 8.5 in every 100,000.

4.4	Assessing data quality	Trials should be critically appraised using the GATE framework, with consideration given to the internal and external validity of the trials. Grades of evidence should be assigned, and assessment undertaken on the applicability of the trials to the New Zealand health sector [known biological factors that may alter effect of pharmaceutical, dependency on way of administration, complex procedure, infrastructure required, other factors]. When high-quality studies are available, these should be the preferred data source when estimating relative treatment effects.	Not visible.	1	Unclear that this has happened.
5.2	Extrapolation of data	Methodology, limitations, and any possible bias associated with extrapolating data should be clearly described in the report and explored through sensitivity analysis. This includes extrapolating data from clinical trials to the longer term (or to final outcomes), generalising results from clinical trials to the NZ clinical setting by taking into account non-compliance, and undertaking indirect comparisons of trials. It is recommended that in the absence of conclusive data, conservative assumptions be used in the analysis.	Where international data are used it is important to include some discussion of the relevance of these data in the New Zealand context. Total population New Zealand lifetables (with equal weighting by gender) were used for the background mortality rate in these models. One table in the model presented data from a New Zealand register of SMA cases by demographics including ethnicity. This data does not appear to have been used in the modelling or in the budget impact assessment.	1	Important to discuss the relevance and suitability of the trial data to the NZ context.
6.1.2	Health benefit to family, whānau, and society	It is recommended that only the HRQOL of the patient being treated should be included in the base-case analysis. If the treatment might have a measurable but indirect impact on the HRQOL of others, such as family and caregivers, this could be estimated and discussed in the report as a scenario.	A major limitation of using a funder perspective in modelling is the lack of any consideration of the considerable care and support by caregivers/whānau of individuals with SMA.	1	SMA likely has a considerable impact on the HRQOL of others around the patient, therefore could have been included as an additional scenario to the base case.
6.2	Health-related quality of life instruments	The NZ EQ-5D Tariff 2 should be referred to first when measuring HRQOL, and should be used to describe the health states. The Global Burden of Disease disability weights and published literature should be used to check for consistency with the estimated EQ-5D values.	Applied.	0	Followed guidance.
6.2.2	Obtaining utility values	If subjective judgement is used to map health states, these health states should be validated through either published literature or expert clinical input. The report should provide a detailed description of the health state and the impact on HRQOL.	There was good discussion provided around the process for deciding on a set of utilities and reflection on the range of utility estimates in the literature, however, there was no discussion about the use of a negative utility (-0.12, health state worse than death) for infantile SMA.	1	Could have explored or explained why there was a negative utility used (controversial in health economics to rank someone's quality of life worse than death).
7.2	Pharmaceutical costs	Should use net pricing from the pharmaceutical supplier, be based on the dose used in the key clinical trials (unless evidence of efficacy for different doses in clinical practice) and take into account the lower price of a future generic pharmaceutical. Dispensing fees and pharmacy mark-up should be included. The cost of co-administered pharmaceuticals and any significant costs with administering the pharmaceutical should also be taken into account.	Hospital schedule, so no dispensing costs etc.	0	Followed guidance.

7.8	Indirect patient costs	Should not be included in cost-utility analyses as costs. Reductions in such costs may be included as health benefits.	None of the models included any complications from lifetime 4 monthly intrathecal infusions of Nusinersen. The clinical trials sourced in the PHARMAC modelling showed a high rate of adverse events (AE) in both the intervention and control (Sham injection) groups for symptomatic infants and children (Finkel et al. 2017; Mercuri et al. 2018). A number AEs were related to SMA making it difficult to distinguish between AEs associated with SMA, the medicine (nusinersen) or complications from intrathecal infusion. Complications of lumbar puncture were noted to be higher in the treatment group than control group in the child onset study (Mercuri et al. 2018). The time frames of the trials were limited to only a few years and additional risks may be expected from repeated infusions (4 monthly for life). Costs likely significant enough that should be considered within the analysis.	2	Potentially significant cost burdens associated with lifetime treatment that have not been considered qualitatively or quantitatively.
7.9	Sourcing and reporting of cost data	Only NZ costs should be used in CUAs. The use of cost data from overseas or clinical trials is not recommended. Expert clinical opinion should be sough regarding likely treatment patterns and applicability of resource use.	In contrast, no discussion was provided around how appropriate it may be to estimate NZ health system costs using data from a 2016 cross sectional study of self-reported health care in Germany (Klug et al. 2016). No adjustment for PPP, just used exchange rate and inflation adjustment. Clear differences in German and New Zealand GDP and basket of goods.	2	Goes against guidance without any reason as to why PPP has not been used, or why NZ costs could not be sourced.
10.1	Parameter uncertainty	Sensitivity analysis should include univariate (simple) analysis and multivariate analysis… any uncertainty in the analysis should be fully tested and described in the report.	The model itself included sensitivity analyses of selected clinical parameters (in the pre-symptomatic model), utilities, pharmaceutical costs, time horizon, other costs and in the symptomatic model conversion rates (to a state with improved outcomes, e.g. SMA type III). We note there were no sensitivity analyses presented exploring the impacts of alternative scenarios of treatment completion, including cessation of treatment, on modelled costs or QALYs gained.	1	Could have explored different scenarios.

Comparison of pembrolizumab against the Pharmac PFPA

Effectively, this acts as an audit of the different medicines against the Pharmac PFPA to assess deviations from recommended methodology. It also allows us to rank from 0 - 3 on a scale of severity of "error" (0 where it is adequate, 1 being a deviation but not likely to have made a difference to the decision, 2 being a deviation that should be noted and may be material, and 3 being a deviation that is material and significant).

Section #	Section header	General description	Pembrolizumab (lung cancer)	Score	Comments	Pembrolizumab (melanoma)	Score	Comments
3.1	Models	Models should avoid unnecessary complexity and should be transparent, well described, and reproducible.	The CUA models did not account for health equity in their structure, data inputs or outputs. Within the prioritisation dossiers, lung cancer is identified as a "Māori health area of focus". Under the heading of "Māori health need", it is noted that Māori have higher incidence and mortality from lung cancer in New Zealand. The prioritisation dossier, TAR and models give inadequate consideration to the inequities in lung cancer burden for Māori, in particular the differing epidemiology and histology of lung cancers for Māori and the impact of inequities in healthcare impacting on current care and the proposed criteria for the use of pembrolizumab for metastatic NSCLC.	3	There are clear health inequities that exist in lung cancer treatment that have not been considered within the models. No separate analysis conducted, and no recognition of differing health need.	The TAR provides good overview of the economic model used.	0	Followed guidance.
3.1.1	Model transparency	Model inputs and assumptions need to be clearly stated and the rationale for the inputs and assumptions documented and explained.	In order to make any assessment of whether pembrolizumab is likely to improve the vast disparities in lung cancer outcomes for Māori, it is critical to understand whether Māori would have **equity in eligibility** for this treatment. Within the provided documents, there is no estimate of the number of Māori with metastatic NSCLC (EGRF and ALK negative) with and without the criterion of PB-L1>50, that might be eligible for pembrolizumab under the proposed funding criteria. Therefore, while addressing an area of focus and high priority for Māori, we are unable to assess whether this treatment will provide equitable benefits for Māori. Adverse events (including those categorised as serious and severe) were common in the clinical trials for both the intervention (pembrolizumab) and comparator groups (Paz Ares et al. 2018; Gandhi et al. 2018; Reck et al. 2016). For example, in the Paz Ares 2018 clinical trial of combination first line therapy, 69.8% and 68.2% of patients in the intervention and comparator groups respectively experienced severe adverse events. Adverse events from pembrolizumab were not included in the base models.	3	Exploration required about existing barriers to access for treatments.	Inputs and assumptions defined in the TAR, hazard ratios from literature, assumptions about efficacy of dosages from relevant CT. Recommendation was made by PTAC and CaTSoP in late 2015 to fund pembrolizumab on low priority, funding recommendation made in mid-2016 by board for pembrolizumab as an additional treatment for late-stage melanoma. Recommendation for low priority only seemingly on the basis of an early evidence base and uncertainty about the medicine's longer term benefits, as well as potential risks and very high cost. No consideration about DHB capacity, and unclear whether the decision to fund the medicine was influenced at all by the fact this is not a high priority area for Māori.	2	Need for exploration into capacity issues.
3.2	Time horizon and cycle length	The report should always justify the time horizon used in the analysis.	20-years stated as the time horizon.	1	It is unclear what the justification for this was, based on the documents alone.	Justification for time horizon 40 years because it is significantly beyond the life expectancy of the patient population. Cycle of 3 weeks reported, since all three treatments (dacarbazine (current), ipilimumab (indirect comparator), pembrolizumab (test)) are administered in 3-week treatment cycles.	1	It is unclear what the justification for this was, based on the documents alone.
3.4	Target population	Target population is the NZ population most likely to receive treatment. It may be necessary to use subgroup analyses if treatment can not be targeted to those most likely to benefit... In cases where the subgroup was defined retrospectively in the clinical trial(s), the data should be used cautiously and evidence of statistical heterogeneity reported.	The clinical trial populations differed in important ways to the Māori population, for example the clinical trial participants were mostly male (59-81%) (Gandhi et al. 2018; Herbst et al. 2016; Paz Ares et al. 2018; Reck et al. 2016) whereas 56% of all lung cancers in Māori are in Māori females (Ministry of Health. 2018). In addition, Māori are diagnosed with lung cancer at a younger median age than non-Māori (Lawrenson et al. 2018; Te Aho o Te Kahu). The impacts of these differences were not considered in the CUA or supporting documentation. no information on the epidemiology of the relevant types of lung cancer indicated for pembrolizumab is provided by ethnicity or considered for inequities, namely NSCLC (squamous and non-squamous). The PHARMAC TAR notes that NSCLCs comprise most (80%) of all lung cancers. This data is unreferenced. NZ data for 2015-2018 show that NSCLC comprise 70% of all lung cancers (Te Aho o Te Kahu. 2021), and this is slightly lower for Māori at 66%. In addition, PHARMAC documentation fails to provide context in relation to access to care. For example, PHARMAC have previously noted that access to treatments for cancers for Māori is a particular area of concern, with Māori 35% less likely to receive medicines for the treatment of cancers than non-Māori (adjusted for age and disease burden) (Metcalf et al. 2018). Relevant to this, the modelling does not consider the potential to optimise equity within existing treatment options or the impact of inequities in first line treatments when modelling pembrolizumab as a second line treatment. Pembrolizumab has been shown to provide clinical benefit in improved overall and progression-free survival regardless of PD-L1 level (including PD-L1 negative) (Paz Ares et al. 2018; Gandhi et al. 2018). However, within the TAR, as a method for reducing the fiscal burden of pembrolizumab, it was proposed to limited eligibility to those with high levels of PD-L1>50 (representing about 25-30% of the clinical trial populations) based upon some (but inconsistent) evidence of a greater survival benefit seen for this group in overall survival (Paz Ares et al. 2018; Herbst et al. 2016) and progression free survival (Gandhi et al. 2018). This suggestion is made without any information on the distribution of PD –L1 levels in Māori to ensure that such a requirement does not inequitably impact on access to this medication for Māori. Within the TAR it is acknowledged that PD-L1 testing is an invasive procedure (requiring a tissue sample) and may be variably used by clinicians (estimated at 10%) if not required as a part of the special authority. There is no consideration of the impact of known inequities in access to and quality of healthcare for lung cancer for Māori (Stevens et al. 2008; Te Aho o Te Kahu. 2021), on the likely rates of PD-L1 testing, and subsequent eligibility for pembrolizumab under this proposal.	3	Exploration of the suitability of the trial findings to a seemingly very different population required. The impacts of poor generalisability are not well socialised throughout the documents.	Target population identified.	0	Followed guidance.
3.5	Comparator(s)	Comparator(s) used in analyses should be the funded treatment that most prescribers or clinicians would replace in NZ clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace).	Docetaxel as the comparator for one line, another comparator arm too because of ill fitness. Explained within TAR.	0	Followed guidance.	The analysis of pembrolizumab was indirect since there were no trials comparing pembrolizumab to the active treatment (dacarbazine) in the treatment naïve unresectable or metastatic melanoma population.	2	The appropriateness and implications of this indirect analysis do not seem to have been discussed in depth within the documents provided by Pharmac.
4.1	Data sources	All appropriate levels of evidence should be identified; however, well-conducted RCTs and meta-analyses are the preferred data sources when estimating relative treatment effects. In the absence of valid RCTs, evidence from the highest available level of study design should be considered with reference to the limitations of the study design.	Summary of international trials and literature regarding pembrolizumab for lung cancer within the TAR.	1	Unclear that the evidence has gone through a ranking process to identify the best suited.	The New Zealand Cancer Registry reports the number of melanoma patients, however does not capture information on progression through stages. Pharmac therefore used a surrogate for likely number of patients eligible for treatment, based off New Zealand Cancer Registry numbers of melanoma patients. Pharmac provided some brief commentary on the high uncertainty with this estimate.	0	Followed guidance.
4.4	Assessing data quality	Trials should be critically appraised using the GATE framework, with consideration given to the internal and external validity of the trials. Grades of evidence should be assigned, and assessment undertaken on the applicability of the trials to the New Zealand health sector [known biological factors that may alter effect of pharmaceutical, dependency on way of administration, complex procedure, infrastructure required, other factors]. When high-quality studies are available, these should be the preferred data source when estimating relative treatment effects.	Not visible.	1	Unclear whether this has happened.	Not visible.	1	Unclear whether this has happened.

5.2	Extrapolation of data	Methodology, limitations, and any possible bias associated with extrapolating data should be clearly described in the report and explored through sensitivity analysis. This includes extrapolating data from clinical trials to the longer term (or to final outcomes), generalising results from clinical trials to the NZ clinical setting by taking into account non-compliance, and undertaking indirect comparisons of trials. It is recommended that in the absence of conclusive data, conservative assumptions be used in the analysis.	The modelling drew on international trial data for the starting proportions of the population on different treatment regimes, and transitions to: further treatments, supportive care and death. In addition, the main outcomes of overall survival and progression free survival for both the intervention arm (pembrolizumab) and the comparator arms of usual care come from trial data. There was no discussion provided on the relevance of these estimates in the New Zealand healthcare context for the New Zealand population, or for Māori specifically. New Zealand lung cancer survival rates are worse than a number of countries with comparable health systems (Lawrenson et al. 2018, Coleman et al. 2011). In addition, there are known disparities in lung cancer survival for Māori overall, by stage, and of particular relevance to pembrolizumab, Māori with distant disease are 30% more likely to die than non-Māori (with the same stage), HR 1.298 (95%CI 1.226- 1.374) (Gurney et al. 2020). The worse survival in New Zealand, and for Māori, means that there is the potential for pembrolizumab to achieve even greater benefits at the population level than demonstrated in clinical trials. The assumptions around cancer survival in the model are important as sensitivity analyses indicated that the models were most sensitive to assumptions around overall survival and the cost of pembrolizumab.	3	As above, this requires exploration around the suitability of the findings to the New Zealand context, specifically for groups already facing inequities in access to health care and also health outcomes.	Explanation of CT that informed model provided. Limitation around oncology infusion capacity mentioned, but not well discussed in terms of the risk of capacity not increasing. No discussion about what happens if there isn't the capacity, or what it would mean for the NZ clinical environment.	2	Exploration needed into the feasibility of increasing capacity for oncology infusion, as well as the potential disbenefits that could eventuate if capacity is not extended.
6.1.2	Health benefit to family, whānau, and society	It is recommended that only the HRQOL of the patient being treated should be included in the base-case analysis. If the treatment might have a measurable but indirect impact on the HRQOL of others, such as family and caregivers, this could be estimated and discussed in the report as a scenario.	Not captured.	1	Could be explored as an alternative scenario, particularly through literature that has observed care burden for cancer patients.	The analysis conducted by Pharmac assumed there would be the capacity to meet the extra demand for oncology infusion services, however this did not seem to be a well tested assumption throughout the analysis (i.e. is it feasible for DHBs to increase their infusion capacity?). The implications of funding a medicine without having the capacity to administer it have not been well captured. The potential disbenefits also of closing out other infusion treatments for other diseases are not well captured either.	2	See above.
6.2	Health-related quality of life instruments	The NZ EQ-5D Tariff 2 should be referred to first when measuring HRQOL, and should be used to describe the health states. The Global Burden of Disease disability weights and published literature should be used to check for consistency with the estimated EQ-5D values.	Use of EurQOL Eq-5D instrument. Based off Chouaid et al., 2013.	1	Unclear whether this is appropriate, or a good substitute for the NZ EQ-5D Tariff 2.	Used.	0	Followed guidance.
6.2.2	Obtaining utility values	If subjective judgement is used to map health states, these health states should be validated through either published literature or expert clinical input. The report should provide a detailed description of the health state and the impact on HRQOL.	The utilities of progression-free disease (0.58) and progressive disease (0.70) came from a study of the quality-of-life preferences of patients with metastatic NSCLC from 25 hospitals across Europe, Canada, Australia and Turkey (Chouaid et al. 2013). The authors of this paper comment on the higher values of utilities from their study compared to other studies and consider the difference is due to the important influence of "elicitation method, the difference in study population (patients versus general public), or a combination of both". This is an important point when considering the comparability of the utilities used by PHARMAC across different CUA models.	2	Needs further discussion/exploration on why or why not this is appropriate for the Pharmac analysis.	Utility weights calculated compared to literature - similar in size.	0	Followed guidance.
7.2	Pharmaceutical costs	Should use net pricing from the pharmaceutical supplier, be based on the dose used in the key clinical trials (unless evidence of efficacy for different doses in clinical practice) and take into account the lower price of a future generic pharmaceutical. Dispensing fees and pharmacy mark-up should be included. The cost of co-administered pharmaceuticals and any significant costs with administering the pharmaceutical should also be taken into account.	In the calculation of pharmaceutical costs, the TAR notes that PHARMAC modelling used international clinical trial data on the proportions of patients on different lung cancer medicine treatments to estimate current care and applied NZ medicine costs to these distributions. There is no discussion on whether these treatment proportions reflect current (best practice or actual) patterns of lung cancer treatment New Zealand.	2	Requires assessment of whether this is the appropriate and whether there are likely to be material differences in costs given potential differences in treatment proportions.	Seemingly fine. Costs of administration taken into account, accommodation for wastage, mark-up, etc.	0	Followed guidance.
7.8	Indirect patient costs	Should not be included in cost-utility analyses as costs. Reductions in such costs may be included as health benefits.	Not visible.	1	Unclear whether there has been inclusion of reductions in indirect patient costs as health benefits.	Not included. No discussion of the adverse events recognised in the trial.	1	Consideration of adverse events important, even qualitatively.
7.9	Sourcing and reporting of cost data	Only NZ costs should be used in CUAs. The use of cost data from overseas or clinical trials is not recommended. Expert clinical opinion should be sough regarding likely treatment patterns and applicability of resource use.	Use of Pharmac Cost Resource Manual to estimate the other costs of treatment (outside of pharmaceutical cost).	0	Followed guidance.	Use of Pharmac Cost Resource Manual to estimate the other costs of treatment and health sector costs.	0	Followed guidance.
10.1	Parameter uncertainty	Sensitivity analysis should include univariate (simple) analysis and multivariate analysis… any uncertainty in the analysis should be fully tested and described in the report.	Sensitivity analyses were run to examine the additional costs of adverse events, but there was no consideration of the health impacts or (disutility) of experiencing an adverse event.	1	Exploration of the severity of adverse events and the associated costs important for robustness of analysis.	The model itself included sensitivity analyses of selected clinical parameters, utilities, pharmaceutical costs, time horizon, and other costs.	0	Followed guidance.

Comparison of empagliflozin against the Pharmac Factors For Consideration (FFC) Internal Guidance Document

Effectively, this acts as an audit of the different medicines against the Pharmac FFC Internal Guidance Document to assess deviations from recommended methodology. It also allows us to rank from 0 - 3 on a scale of severity of "error" (0 where it is adequate, 1 being a deviation but not likely to have made a difference to the decision, 2 being a deviation that should be noted and may be material, and 3 being a deviation that is material and significant).

Section	Sub-section	Description	Empagliflozin	Score	Comments
Need	**Health need of the person**	How unwell is a person with the health condition compared with an individual in perfect health? All significant health effects, physical and mental, are relevant and are taken into account when estimating health need. This may include comorbidities. Important to note, health need of individuals is not included in the CUA undertaken by Pharmac. It is simply a measurement of the disease burden irrespective of treatments already available or proposed. Health need of populations are however included in BIA, **and sometimes in CUA**. Assumedly, this would enter CUA when there is recognition of significant differences in prevalence across different population groups; as seen here in diabetes.	Recognised within the documents that diabetes has serious long-term consequences, including cardiovascular complications and disease burden, and that occurrence and rate of progression of diabetes is notably higher for high risk populations (Māori, Pacific, South Asians). T2DM often leads to cardiovascular disease in respect to morbidity and mortality. There was no separate CUA done, despite recognition that the health need likely differs significantly for high risk populations. Within the prioritisation dossier, diabetes is noted to be a Māori health area of focus. Māori are also noted to have higher rates of diabetes, CVD and diabetes associated complications. The average age of diabetes is noted to be lower in Māori than in non-Māori. Inequities in access to care for diabetes, including diagnosis and any potential inequities in pharmaceutical access, were not discussed. The differing epidemiology of diabetes and CVD in Māori have not been taken into consideration within the PHARMAC modelling of empagliflozin. At a minimum we would expect to see some discussion of how generalizable the RCT results (and the CUA) are to the NZ total population with diabetes, and separately to the Māori population with diabetes. We expect that there are large differences between the RCT population and the Māori population, at least with respect to age and access to healthcare impacting on diagnosis of CVD and access to existing diabetes treatments, and likely also important differences between the RCT and the total NZ population (including gender proportions) that are critical to consider in the presentation and interpretation of the modelling results.	3	Discussion on generalisability and analysis do not fully explore key issues about the potential impact for Māori.
	Availability and suitability of existing medicines, medical devices, and treatments	What options are currently publicly funded to treat the population with this condition? How well do they work? A medicine is generally considered available if it is listed on the Schedule for the relevant indication. Consideration of the practicality, effectiveness, appropriateness of the treatment in the population group is necessary. this does come into the CUA because the CUA compares the proposal with current practice. The CUA focuses on net incremental benefit, however, so may not capture all the details of current treatment described under the Health Need Factor.	Current treatments are outlined in the TAR. Issues of current accessibility and suitability, particularly for high risk populations, are not discussed i.e. are Māori, Pacific, South Asians able to access existing treatments?	2	No exploration of existing barriers and inequities in access to diabetes treatments. Descriptive analysis only of current state.
	Health need of the family, whanau, and wider society	What are the health needs for the family, whanau of the person with the disease, and the health needs for wider society? Considers the effect of a person's illness on the health of those around them. CUA may in some cases take into account the health need of others.	Prioritisation dossier states that long-term poor management of diabetes is associated with a range of severe complications and premature death, and that has an impact on family and whanau if an individual with diabetes requires care or if those around them require care from others.	1	No exploration of the implications this has for those around someone with diabetes. Amputations, kidney disease, etc. Literature out there that explores this, would hope Pharmac would do something like this.
	Impact on Māori health areas of focus and Māori health outcomes	Has the disease, condition, or illness been identified as a Māori health area of focus? What is the impact on Māori health outcomes? This considers the diseases outlined in the Te Whaioranga 2013 - 2023: Māori Responsiveness Strategy. Areas are diabetes and renal disease, respiratory disease (asthma, COPD, lung disease), heart/cardiovascular, mental health, arthritis and gout, obesity, rheumatic fever. In general this doesn't enter CUA estimates. However, the guidance states that a CUA can be undertaken for different sub-groups, particularly where value for money for a population group experiencing a disparity is likely to be significant.	Recognised that Māori have significantly higher rates of diabetes, CVD, and diabetes associated complications than non-Māori populations. Average age of diabetes among Māori is significantly younger than non-Māori. Māori health area of focus within strategy.	3	Despite recognition of the higher prevalence for Māori, no separate analyses conducted.
	Impact on the health outcomes of population groups experiencing health disparities	What is the impact of the disease/condition on other population groups already experiencing disparities? To what extent does the disease disproportionately affect population groups that have substantive health disparities? This includes Pacific peoples, refugees, LGBTQI+, NZ deprivation deciles 9-10, sub-regionally deprived communities. The illness/disease/condition itself is not a sufficient way to define a group. **Guidance states that a CUA can be undertaken for different sub-groups, particularly where value for money for a population group experiencing a disparity is likely to be significant.**	Recognised greater disease burden in South Indian, Māori, and Pacific populations in NZ, as well as people in areas of low socioeconomic status and people with a long-history of mental illness - noted to have higher diabetes/CVD disease burden. Includes higher incidence of diabetes as well as complications from diabetes.	3	Despite recognition of the higher prevalence for Māori + Pacific, no separate analyses conducted.
	Impact on govt. health priorities	Overarching govt. priorities are child wellbeing, mental wellbeing, prevention, health equity, primary health care, with specific focus on rare diseases, cancer, long-term conditions, and infectious diseases. This does not enter the CUA.	Proposed intervention helps to prevent, intervene, rehabilitate, and improve wellbeing of people with long-term disease.	0	Followed guidance.
Benefit	**Health benefit to the person**	What would be the health benefits or losses to the person who would receive the medicine? Looking at the net benefits over and above what is achieved by current treatments, including extension of life as well as improved HRQOL. As well as health benefits, **potential losses as a result of the funding decision should be considered. This includes harm done by adverse effects as well as no longer providing a gain that current treatment delivered.** Enters the CUA directly.	Health benefits well discussed in the TAR, based off the EMPAG-Reg trial. PTAC did not comment on the strength and quality of evidence, however. Adverse events not considered in the model as the incremental difference between the two therapies and the relative cost of treating the most frequently occurring adverse events was considered to be immaterial, as per Hot Topic meeting July 2019.	1	Adverse effects documented, but not modelled.

	Health benefit to the family, whanau, and wider society	What would be the health benefits for the family, whanau, or wider society of the person receiving treatment? Only clinically significant health benefits should be counted here - judgement required as to what is clinically significant. Benefits to others not usually counted in CUA, unless vaccines and herd immunity.	Prevention of premature death and reduced likelihood of being hospitalised for heart failure, benefit to family and whanau. Not included in CUA.	0	Followed guidance.
	Consequences for the health system	If the proposal was funded, what would be the consequences for the health system? Does it relate to any govt. priorities? Includes relieving or increasing pressure on the health system. **Flow-on effects may be complicated and their perceived presence should be justified or made clear that they are hypothetical.** Generally not included in CUA.	Reduction in heart failure hospitalisations, initiation of insulin, progression to macroalbuminuria, and renal replacement. Reduction of cost to the healthcare system. Calculated and included in the CUA.	0	Followed guidance.
Costs and savings	**To the person**	What would the health-related costs and savings be to the person who would be treated? Regardless of whether the patient pays it or it is subsidised by Vote Health. Change in costs and savings over status quo. May include GP visits, dispensing fees, travel costs, co-payments, part charges, care in home, etc. CUA generally only analyses costs that the govt. partially subsidises through the health sector budget. Private costs and savings are excluded from CUA.	Add-on therapy, therefore an increase of four pharmacy co-payments per year, per person. Increase not experienced by patients who start on SGLT-2 in combination with metformin (net change in prescriptions assumed to be 0). GP costs assumed to be 0; patients assumedly will bundle in with existing GP visits that patients would have for diabetes and CVD management.	1	Questions about inequitable access to primary care that could be asked when considering the assumption about being able to bundle GP visits and prescriptions.
	To the family, whanau, and wider society	Defined and considered in the same way as to the individual. Do not consider whether a family is privately funding a treatment for a patient, and any loss of income from inability to work is not included (however, consider inability to work as a loss of usual activities in the Need quadrant, and ability to work as a gain in usual activities in health benefit). Only certain direct healthcare costs are included in CUA, specifically those that the govt. partially subsidise through the health sector budget. Otherwise, costs and savings to family, whanau, and wider society are excluded from CUA.	None identified.	0	Followed guidance.
	To pharmaceutical expenditure	How would funding the proposal impact pharma expenditure? Would fund it result in savings from switching from already funded pharmaceuticals? Net effect. Covers Combined Pharmaceutical Budget (CPB) and both hospital medicines and devices. Enters CUA.	Identified and broken down within the TAR.	0	Followed guidance.
	To the rest of the health system	Potential costs and savings that funding the proposal may have for the rest of the health system. Net effect. Not to be confused with health benefit consequences for the system. Defines health system as being Vote Health funding where that funding is enabling the delivery of health services. Includes DHBs, and any other services which are funded via Vote Health. Enters CUA.	Potential savings discussed in the TAR and dossier; through reduction in heart failure hospitalisations and initiation of renal replacement therapy associated with SGLTi therapy. Use of NZ costs.	0	Followed guidance.
Suitability	**Features of the medicine that impact on use by the person**	What features may impact use by the person receiving the medicine? Is it registered for the disease or disorder that funding is being sought for? Includes issues that may make use difficult, less effective, or dissuade or prevent people from using it altogether. Can include size, shape, taste, method of delivery, ease of use, time required, packaging, supporting info, training. Subgroups particularly important to consider. **While this is likely to be reported with qualitative data, evidence is still required. If possible, compare with the suitability of existing treatments to show the size of the improvement or worsening.** Can affect a CUA result, but indirectly. **If significant enough to impact health benefits, will be included in CUA. Common example is when cost-effectiveness depends on the assumptions made about adherence and the costs and benefits and likelihood of an adherence programme affect use.**	Increase in pill burden of population with already high pill burden. Seemingly no indication if this is significant or would pose issues.	1	Could ask the question about whether there will be decreases in medicine adherence as consequence of having more pills.
	Features that impact on use by family, whanau, and wider society	Are there certain features of the medicine which could impact on health outcomes if it has to be given by someone other than the patient? Same as above about entering CUA.	None identified.	0	Followed guidance.
	Features that impact on use by health workforce	Considering instances where members of the health workforce administer a medicine or medical device to a person. Considers how easy it is for a health worker to use, how likely it is a health worker could make an error. Could even include features which dissuade workers from using a product at all even though it could be clinically beneficial. Indirectly affects CUA.	None identified.	0	Followed guidance.

Comparison of venlafaxine against the Pharmac Factors For Consideration (FFC) Internal Guidance Document

Effectively, this acts as an audit of the different medicines against the Pharmac FFC Internal Guidance Document to assess deviations from recommended methodology. It also allows us to rank from 0 - 3 on a scale of severity of "error" (0 where it is adequate, 1 being a deviation but not likely to have made a difference to the decision, 2 being a deviation that should be noted and may be material, and 3 being a deviation that is material and significant).

Section	Sub-section	Description	Venlafaxine	Score	Comments
Need	**Health need of the person**	How unwell is a person with the health condition compared with an individual in perfect health? All significant health effects, physical and mental, are relevant and are taken into account when estimating health need. This may include comorbidities. Important to note, health need of individuals is not included in the CUA undertaken by Pharmac. It is simply a measurement of the disease burden irrespective of treatments already available or proposed. Health need of populations are however included in BIA, **and sometimes in CUA**. Assumedly, this would enter CUA when there is recognition of significant differences in prevalence across different population groups.	Board paper (only documents received) do not discuss the health need in terms of severity and requirements.	0	Explanation of the health need important for provision of context.
	Availability and suitability of existing medicines, medical devices, and treatments	What options are currently publicly funded to treat the population with this condition? How well do they work? A medicine is generally considered available if it is listed on the Schedule for the relevant indication. Consideration of the practicality, effectiveness, appropriateness of the treatment in the population group is necessary. this does come into the CUA because the CUA compares the proposal with current practice. The CUA focuses on net incremental benefit, however, so may not capture all the details of current treatment described under the Health Need Factor.	Board paper shows the alternatives that are funded. No mention of how well they work, current access and/or issues with them regarding suitability and availability, particularly for those facing disproportionate mental health outcomes. Māori health and Māori health equity considerations are also relevant across other FFC but are not considered in any of these. The (disproportionately) large amount of consideration, concern, and planning for those resistant to a brand switch compared to the total lack of acknowledgement or concern about the substantial under prescribing of venlafaxine for Māori was revealing.	2	Insights required into current suitability, and whether the brand switch would enhance inequities of access and treatment, or help to address them.
	Health need of the family, whanau, and wider society	What are the health needs for the family, whanau of the person with the disease, and the health needs for wider society? Considers the effect of a person's illness on the health of those around them. CUA may in some cases take into account the health need of others.	Noted to be unchanged.	1	Unclear what was previously provided.
	Impact on Māori health areas of focus and Māori health outcomes	Has the disease, condition, or illness been identified as a Māori health area of focus? What is the impact on Māori health outcomes? This considers the diseases outlined in the Te Whaioranga 2013 - 2023: Māori Responsiveness Strategy. Areas are diabetes and renal disease, respiratory disease (asthma, COPD, lung disease), heart/cardiovascular, mental health, arthritis and gout, obesity, rheumatic fever. In general this doesn't enter CUA estimates. However, the guidance states that a CUA can be undertaken for different sub-groups, particularly where value for money for a population group experiencing a disparity is likely to be significant.	Despite mental health being identified as a "Māori health area of focus" (as outlined in the Te Whaioranga Strategy), little consideration was given to matters relating to Māori health and equity in the brand switch. Any consideration was almost exclusively restricted to the "need" component of the factors for consideration (FFC) which stated that: "*Usage of venlafaxine by Māori is about 8%, which is 50% below the proportion of Māori in the general population. We consider that this proposal is unlikely to have a significant clinical impact on Māori, as patients would continue to have access to a fully funded brand.*" Projected numbers of combined Māori and Pacific patients on venlafaxine for 2017-2019 were provided in the initial 'Summary of the Pharmaceutical' table of the board papers and appears to be a simple calculation of 8% of the projected total number of people. We note this is different from the above statement whereby Māori are estimated at 8% (not Māori and Pacific). The figures given suggest that Māori are under-represented in the prescribing and/or dispensing of venlafaxine, although this is only implied (not explicitly stated or interpreted) with the comment that 8% is less than 50% of the population proportion of Māori. The use of a single crude measure of health need for Māori provides limited ability to determine inequities in venlafaxine by ethnicity. Comparing to population proportions fails to take into consideration the greater burden of mental health experienced by Māori (Ministry of Health), any impact of the different age structures of Māori and Pākehā, or the known unmet need for venlafaxine and other antidepressants/anxiolytics among Māori (Metcalf et al. 2018). Evidence shows Māori are 60% more likely than non-Māori adults (age-standardised) to report high or very high probability of having an anxiety or depressive disorder (Ministry of Health). In contrast, Māori are 52% less likely than NZ European/Other (age-adjusted) to be dispensed venlafaxine (Metcalf et al. 2018). Māori also have lower receipt for all other major antidepressants and anxiolytics even when age and burden of disease is taken into account (Metcalf et al. 2018). Importantly there is a lack of context in relation to Māori health and inequities in conditions where venlafaxine is indicated or any context of likely inequities in access to healthcare, diagnosis, and treatment for such indications. Assuming the brand switch "is unlikely to have a significant clinical impact on Māori" indicates that inequities in access to venlafaxine for Māori will continue. These projected numbers (and subsequent costs) do not consider the potential unmet need and possible increased numbers of Māori that could result if access to and quality of care was equitable for Māori. Indeed, increased accessibility to Venlafaxine may be possible with the change from the restricted supply of Efexor XR to an unrestricted supply of Enlafax XR with stat dispensing.	3	Thorough consideration required of the wider equity issues that surround mental health and access to health services. About missed opportunity.
	Impact on the health outcomes of population groups experiencing health disparities	What is the impact of the disease/condition on other population groups already experiencing disparities? To what extent does the disease disproportionately affect population groups that have substantive health disparities? This includes Pacific peoples, refugees, LGBTQI+, NZ deprivation deciles 9-10, sub-regionally deprived communities. The illness/disease/condition itself is not a sufficient way to define a group. **Guidance states that a CUA can be undertaken for different sub-groups, particularly where value for money for a population group experiencing a disparity is likely to be significant.**	See above.	3	See above.
	Impact on govt. health priorities	Overarching govt. priorities are child wellbeing, mental wellbeing, prevention, health equity, primary health care, with specific focus on rare diseases, cancer, long-term conditions, and infectious diseases. This does not enter the CUA.	Falls into govt. priorities. Brief discussion, but more about brand switch management, rather than mental wellbeing importance and focus.	0	Somewhat followed guidance.
Benefit	**Health benefit to the person**	What would be the health benefits or losses to the person who would receive the medicine? Looking at the net benefits over and above what is achieved by current treatments, including extension of life as well as improved HRQOL. As well as health benefits, **potential losses as a result of the funding decision should be considered. This includes harm done by adverse effects as well as no longer providing a gain that current treatment delivered.** Enters the CUA directly.	Not discussed.	1	Important exploration, given potential for increasing pill burden and change management risks.
	Health benefit to the family, whanau, and wider society	What would be the health benefits for the family, whanau, or wider society of the person receiving treatment? Only clinically significant health benefits should be counted here - judgement required as to what is clinically significant. Benefits to others not usually counted in CUA, unless vaccines and herd immunity.	Assumedly unchanged because of brand switch.	1	Unclear what was previously provided.
	Consequences for the health system	If the proposal was funded, what would be the consequences for the health system? Does it relate to any govt. priorities? Includes relieving or increasing pressure on the health system. **Flow-on effects may be complicated and their perceived presence should be justified or made clear that they are hypothetical.** Generally not included in CUA.	The removal of special authority and introduction of stat dispensing may impact on access to venlafaxine but was not assessed.	1	Important consideration, since it may mean people can access easier.
Costs and savings	**To the person**	What would the health-related costs and savings be to the person who would be treated? Regardless of whether the patient pays it or it is subsidised by Vote Health. Change in costs and savings over status quo. May include GP visits, dispensing fees, travel costs, co-payments, part charges, care in home, etc. CUA generally only analyses costs that the govt. partially subsidises through the health sector budget. Private costs and savings are excluded from CUA.	Increased costs to patients through co-payments by having to get two dispensings if on 150mg and 75mg (previously 225mg), those on 3x 75mg would not see increase in fees but increased pill burden. Potential benefit recognised however, in terms of reduced transaction costs such as travel by being able to get more tablets at once.	1	Understanding of how many people this might affect would give better insight into whether this is negligible or not.

	To the family, whanau, and wider society	Defined and considered in the same way as to the individual. Do not consider whether a family is privately funding a treatment for a patient, and any loss of income from inability to work is not included (however, consider inability to work as a loss of usual activities in the Need quadrant, and ability to work as a gain in usual activities in health benefit). Only certain direct healthcare costs are included in CUA, specifically those that the govt. partially subsidise through the health sector budget. Otherwise, costs and savings to family, whanau, and wider society are excluded from CUA.	No discussion.	1	Important to consider, even qualitatively.
	To pharmaceutical expenditure	How would funding the proposal impact pharma expenditure? Would fund it result in savings from switching from already funded pharmaceuticals? Net effect. Covers Combined Pharmaceutical Budget (CPB) and both hospital medicines and devices. Enters CUA.	Interestingly, the estimated savings to the expenditure over time have been discounted at a rate of 8%, which is well above the recommended 3.5% in the PFPA. This in turn underestimates the savings.	1	No reason provided for the use of a different discount rate. Discussion needed if for a valid reason.
	To the rest of the health system	Potential costs and savings that funding the proposal may have for the rest of the health system. Net effect. Not to be confused with health benefit consequences for the system. Defines health system as being Vote Health funding where that funding is enabling the delivery of health services. Includes DHBs, and any other services which are funded via Vote Health. Enters CUA.	Interestingly, the estimated savings to the expenditure over time have been discounted at a rate of 8%, which is well above the recommended 3.5% in the PFPA. This in turn underestimates the savings.	1	See above.
Suitability	**Features of the medicine that impact on use by the person**	What features may impact use by the person receiving the medicine? Is it registered for the disease or disorder that funding is being sought for? Includes issues that may make use difficult, less effective, or dissuade or prevent people from using it altogether. Can include size, shape, taste, method of delivery, ease of use, time required, packaging, supporting info, training. Subgroups particularly important to consider. **While this is likely to be reported with qualitative data, evidence is still required. If possible, compare with the suitability of existing treatments to show the size of the improvement or worsening.** Can affect a CUA result, but indirectly. **If significant enough to impact health benefits, will be included in CUA. Common example is when cost-effectiveness depends on the assumptions made about adherence and the costs and benefits and likelihood of an adherence programme affect use.**	In particular, possible challenges with the brand switch were raised and mitigating initiatives proposed, but these failed to consider implications for or opportunities to address Māori health and equity. Venlafaxine was recognised as a difficult brand switch for a range of reasons. These included the large number of people affected, the assumed "vulnerable and change resistant" patient group, and the high proportion of people with long-term use. In addition, brand loyalty and increased pill burden (with the delisting of 225mg tablets) were also raised. Suggested strategies to mitigate these challenges included an implementation plan with appropriate communication for patients and health professionals; a brand switch fee for pharmacists to assist with the increased support patients may need with the brand switch; and an alternative brand allowance clause that would allow a few patients more time to transition to a new brand. Māori health was not considered in any of these e.g. was there a higher proportion of Māori on Efexor or 225mg tablets? Importantly, Māori health was not considered in any recommended strategies to assist with the brand switch e.g. there was a missed opportunity in communication with the sector on addressing inequities in access to venlafaxine for Māori. We also note that the minutes of the PHARMAC evaluation committee state with regard to FFC that, "particular emphasis will be given to those aspects of Tender Bids which demonstrate "health outcomes", and those aspects of Tender Bids which demonstrate the impact on the "funding provided" for pharmaceuticals". This suggests that need (where Māori health is located) may be given less weight than funding and health outcomes. Finally, there was no Māori health expertise required in the member roles of the PHARMAC evaluation committee that considered this tender.	3	Thorough consideration required of the wider equity issues that surround mental health and access to health services.
	Features that impact on use by family, whanau, and wider society	Are there certain features of the medicine which could impact on health outcomes if it has to be given by someone other than the patient? Same as above about entering CUA.	Not discussed.	1	Unclear what was previously provided.
	Features that impact on use by health workforce	Considering instances where members of the health workforce administer a medicine or medical device to a person. Considers how easy it is for a health worker to use, how likely it is a health worker could make an error. Could even include features which dissuade workers from using a product at all even though it could be clinically beneficial. Indirectly affects CUA.	Not discussed.	1	Unclear what was previously provided.

Comparison of ustekinumab against the Pharmac Factors For Consideration (FFC) Internal Guidance Document

Effectively, this acts as an audit of the different medicines against the Pharmac FFC Internal Guidance Document to assess deviations from recommended methodology. It also allows us to rank from 0 - 3 on a scale of severity of "error" (0 where it is adequate, 1 being a deviation but not likely to have made a difference to the decision, 2 being a deviation that should be noted and may be material, and 3 being a deviation that is material and significant).

Section	Sub-section	Description	Ustekinumab	Score	Comments
Need	**Health need of the person**	How unwell is a person with the health condition compared with an individual in perfect health? All significant health effects, physical and mental, are relevant and are taken into account when estimating health need. This may include comorbidities. Important to note, health need of individuals is not included in the CUA undertaken by Pharmac. It is simply a measurement of the disease burden irrespective of treatments already available or proposed. Health need of populations are however included in BIA, **and sometimes in CUA**. Assumedly, this would enter CUA when there is recognition of significant differences in prevalence across different population groups.	Dossier discusses the health need, including a score of 19 (suggesting severe effects of Crohn's and significant reductions in HRQOL).	0	Followed guidance.
	Availability and suitability of existing medicines, medical devices, and treatments	What options are currently publicly funded to treat the population with this condition? How well do they work? A medicine is generally considered available if it is listed on the Schedule for the relevant indication. Consideration of the practicality, effectiveness, appropriateness of the treatment in the population group is necessary. this does come into the CUA because the CUA compares the proposal with current practice. The CUA focuses on net incremental benefit, however, so may not capture all the details of current treatment described under the Health Need Factor.	Discussion in the TAR and dossier about the current treatments and their effectiveness. Limited effectiveness of current treatments and potential side effects which restrict long-term use. No discussion about potential access issues that exist currently.	2	Further exploration required to show why current treatments may not be suitable, and why new treatments may be more suitable, particularly with respect to access.
	Health need of the family, whanau, and wider society	What are the health needs for the family, whanau of the person with the disease, and the health needs for wider society? Considers the effect of a person's illness on the health of those around them. CUA may in some cases take into account the health need of others.	None identified.	0	Followed guidance.
	Impact on Māori health areas of focus and Māori health outcomes	Has the disease, condition, or illness been identified as a Māori health area of focus? What is the impact on Māori health outcomes? This considers the diseases outlined in the Te Whaioranga 2013 - 2023: Māori Responsiveness Strategy. Areas are diabetes and renal disease, respiratory disease (asthma, COPD, lung disease), heart/cardiovascular, mental health, arthritis and gout, obesity, rheumatic fever. In general this doesn't enter CUA estimates. However, the guidance states that a CUA can be undertaken for different sub-groups, particularly where value for money for a population group experiencing a disparity is likely to be significant.	Within the prioritisation dossier, Crohn's disease is not a "Māori health area of focus". Under "Māori health need", it is noted that Crohn's disease is rare in Māori and Pacific. This statement is based upon data from a study in the Canterbury DHB population in 2006, where 1% (n=8) of recruited Crohn's cases were Māori, and no Pacific Crohn's cases were identified and recruited into the study (Gearry et al. 2006). We note that study age-standardised total population rates are compared with Māori crude rates in the PHARMAC documentation. A more recent study through Otago DHB found similarly low rates of Crohn's disease in Māori (n=4) (Coppell et al. 2018). There are some important limitations to the study's findings that are not identified in the prioritisation dossier. Both Otago and Canterbury DHBs have relatively small proportions of Māori (~7% in both Otago and Canterbury versus 15% nationally), limiting the studies abilities to measure incidence and prevalence in Māori with precision. In both studies, recruitment strategies heavily relied upon existing Crohn's diagnoses and engagement with the health system. In the Otago study, cases were identified through hospital records, and in the Canterbury study recruitment onto the study was through GP and hospital clinics (the former by searching for terms relating to Crohn's and known treatments), Crohn's support groups, and more generally such as through newspaper articles and posters. In addition to a likely underestimate of Crohn's in Māori due to the studies recruitment strategies (healthcare based and selecting for more severe illness), there is a known undercount of Māori in health data (NHI) of around 15-20% (Reid et al. 2016; Cleary 2021), and Māori are likely to be differentially impacted by the difficulties in diagnosing Crohn's disease due to inequities in the healthcare system, particularly in access to primary care.	2	Further exploration required to show why current treatments may not be suitable, and why new treatments may be more suitable, particularly with respect to access. Need to be clear about the limitations of the information being used.
	Impact on the health outcomes of population groups experiencing health disparities	What is the impact of the disease/condition on other population groups already experiencing disparities? To what extent does the disease disproportionately affect population groups that have substantive health disparities? This includes Pacific peoples, refugees, LGBTQI+, NZ deprivation deciles 9-10, sub-regionally deprived communities. The illness/disease/condition itself is not a sufficient way to define a group. **Guidance states that a CUA can be undertaken for different sub-groups, particularly where value for money for a population group experiencing a disparity is likely to be significant.**	Stated lower prevalence in Māori and Pacific peoples, but see above.	2	Further exploration required to show why current treatments may not be suitable, and why new treatments may be more suitable, particularly with respect to access.
	Impact on govt. health priorities	Overarching govt. priorities are child wellbeing, mental wellbeing, prevention, health equity, primary health care, with specific focus on rare diseases, cancer, long-term conditions, and infectious diseases. This does not enter the CUA.	Focus because of long-term condition.	0	Followed guidance.

Benefit	**Health benefit to the person**	What would be the health benefits or losses to the person who would receive the medicine? Looking at the net benefits over and above what is achieved by current treatments, including extension of life as well as improved HRQOL. As well as health benefits, **potential losses as a result of the funding decision should be considered. This includes harm done by adverse effects as well as no longer providing a gain that current treatment delivered.** Enters the CUA directly.	Health benefits discussed in PTAC papers, based off clinical trial.	0	Followed guidance.
	Health benefit to the family, whanau, and wider society	What would be the health benefits for the family, whanau, or wider society of the person receiving treatment? Only clinically significant health benefits should be counted here - judgement required as to what is clinically significant. Benefits to others not usually counted in CUA, unless vaccines and herd immunity.	Not discussed or well captured.	1	Further insight into the care burden of people with Crohn's required.
	Consequences for the health system	If the proposal was funded, what would be the consequences for the health system? Does it relate to any govt. priorities? Includes relieving or increasing pressure on the health system. **Flow-on effects may be complicated and their perceived presence should be justified or made clear that they are hypothetical.** Generally not included in CUA.	Positive impacts identified likely because of different administration method - reduce pressure on infusion capacity.	0	Followed guidance.
Costs and savings	**To the person**	What would the health-related costs and savings be to the person who would be treated? Regardless of whether the patient pays it or it is subsidised by Vote Health. Change in costs and savings over status quo. May include GP visits, dispensing fees, travel costs, co-payments, part charges, care in home, etc. CUA generally only analyses costs that the govt. partially subsidises through the health sector budget. Private costs and savings are excluded from CUA.	May be some savings to patients and their families if it reduces the use of infliximab, which require patients to travel to hospital for infusion. Private savings, therefore excluded from CUA.	0	Followed guidance.
	To the family, whanau, and wider society	Defined and considered in the same way as to the individual. Do not consider whether a family is privately funding a treatment for a patient, and any loss of income from inability to work is not included (however, consider inability to work as a loss of usual activities in the Need quadrant, and ability to work as a gain in usual activities in health benefit). Only certain direct healthcare costs are included in CUA, specifically those that the govt. partially subsidise through the health sector budget. Otherwise, costs and savings to family, whanau, and wider society are excluded from CUA.	See above.	0	Followed guidance.
	To pharmaceutical expenditure	How would funding the proposal impact pharma expenditure? Would fund it result in savings from switching from already funded pharmaceuticals? Net effect. Covers Combined Pharmaceutical Budget (CPB) and both hospital medicines and devices. Enters CUA.	Outlined (although redacted); unclear whether this is the net effect or not.	0	Followed guidance.
	To the rest of the health system	Potential costs and savings that funding the proposal may have for the rest of the health system. Net effect. Not to be confused with health benefit consequences for the system. Defines health system as being Vote Health funding where that funding is enabling the delivery of health services. Includes DHBs, and any other services which are funded via Vote Health. Enters CUA.	Included in the CUA.	0	Followed guidance.
Suitability	**Features of the medicine that impact on use by the person**	What features may impact use by the person receiving the medicine? Is it registered for the disease or disorder that funding is being sought for? Includes issues that may make use difficult, less effective, or dissuade or prevent people from using it altogether. Can include size, shape, taste, method of delivery, ease of use, time required, packaging, supporting info, training. Subgroups particularly important to consider. **While this is likely to be reported with qualitative data, evidence is still required. If possible, compare with the suitability of existing treatments to show the size of the improvement or worsening.** Can affect a CUA result, but indirectly. **If significant enough to impact health benefits, will be included in CUA. Common example is when cost-effectiveness depends on the assumptions made about adherence and the costs and benefits and likelihood of an adherence programme affect use.**	Crohn's disease can be a difficult condition to diagnose, and diagnosis is often delayed (BPAC, 2021). This then raises the question of whether the low incidence of Crohn's in Māori is real, or a result of barriers in access to diagnosis. Further to this, there is no assessment of whether Māori with Crohn's disease are receiving best practice care and have had equitable access to the first- and second-line treatments required in order to then access ustekinumab as a second- or third-line treatment. If Māori are known or suspected to be underdiagnosed and undertreated (with existing options), the model should account for this rather than assume ongoing inequities. While it may be reasonable not to model a treatment for Crohn's disease specifically for Māori given it is identified as a rare condition (discussed below), there are a number of important equity issues that required further exploration in the TAR and prioritisation dossier.	2	Further exploration required to understand Crohn's prevalence in Māori and the ability to access diagnostic services.
	Features that impact on use by family, whanau, and wider society	Are there certain features of the medicine which could impact on health outcomes if it has to be given by someone other than the patient? Same as above about entering CUA.	Potentially better suited for patients, family, and whanau because of way it is administered (do not have to access hospital as frequently).	0	Followed guidance.
	Features that impact on use by health workforce	Considering instances where members of the health workforce administer a medicine or medical device to a person. Considers how easy it is for a health worker to use, how likely it is a health worker could make an error. Could even include features which dissuade workers from using a product at all even though it could be clinically beneficial. Indirectly affects CUA.	Likely reduction in hospitalisations, clinician visits for administration, less infusion required compared to infliximab. Not quantified.	0	Followed guidance.

Comparison of nusinersen against the Pharmac Factors For Consideration (FFC) Internal Guidance Document

Effectively, this acts as an audit of the different medicines against the Pharmac FFC Internal Guidance Document to assess deviations from recommended methodology. It also allows us to rank from 0 - 3 on a scale of severity of "error" (0 where it is adequate, 1 being a deviation but not likely to have made a difference to the decision, 2 being a deviation that should be noted and may be material, and 3 being a deviation that is material and significant).

Section	Sub-section	Description	Nusinersen	Score	Comments
Need	**Health need of the person**	How unwell is a person with the health condition compared with an individual in perfect health? All significant health effects, physical and mental, are relevant and are taken into account when estimating health need. This may include comorbidities. Important to note, health need of individuals is not included in the CUA undertaken by Pharmac. It is simply a measurement of the disease burden irrespective of treatments already available or proposed. Health need of populations are however included in BIA, **and sometimes in CUA**. Assumedly, this would enter CUA when there is recognition of significant differences in prevalence across different population groups.	Need across the three disease types discussed in the dossier. Talks about distribution of prevalence too across the different types.	0	Followed guidance.
	Availability and suitability of existing medicines, medical devices, and treatments	What options are currently publicly funded to treat the population with this condition? How well do they work? A medicine is generally considered available if it is listed on the Schedule for the relevant indication. Consideration of the practicality, effectiveness, appropriateness of the treatment in the population group is necessary. this does come into the CUA because the CUA compares the proposal with current practice. The CUA focuses on net incremental benefit, however, so may not capture all the details of current treatment described under the Health Need Factor.	No currently funded treatment, reliant heavily on healthcare like physiotherapy. Indirectly shown in CUA through the big QALY gains.	0	Followed guidance.
	Health need of the family, whanau, and wider society	What are the health needs for the family, whanau of the person with the disease, and the health needs for wider society? Considers the effect of a person's illness on the health of those around them. CUA may in some cases take into account the health need of others.	Reliant heavily on carers etc. - current negative impact on the health of those around. Not in CUA.	1	Potential to explore the need of those around the patients given the significant care burden associated with SMA.
	Impact on Māori health areas of focus and Māori health outcomes	Has the disease, condition, or illness been identified as a Māori health area of focus? What is the impact on Māori health outcomes? This considers the diseases outlined in the Te Whaioranga 2013 - 2023: Māori Responsiveness Strategy. Areas are diabetes and renal disease, respiratory disease (asthma, COPD, lung disease), heart/cardiovascular, mental health, arthritis and gout, obesity, rheumatic fever. In general this doesn't enter CUA estimates. However, the guidance states that a CUA can be undertaken for different sub-groups, particularly where value for money for a population group experiencing a disparity is likely to be significant.	Not applicable - reasonable since such small data on SMA and no information on across ethnicity differences in prevalence and burden of illness.	0	Followed guidance.
	Impact on the health outcomes of population groups experiencing health disparities	What is the impact of the disease/condition on other population groups already experiencing disparities? To what extent does the disease disproportionately affect population groups that have substantive health disparities? This includes Pacific peoples, refugees, LGBTQI+, NZ deprivation deciles 9-10, sub-regionally deprived communities. The illness/disease/condition itself is not a sufficient way to define a group. **Guidance states that a CUA can be undertaken for different sub-groups, particularly where value for money for a population group experiencing a disparity is likely to be significant.**	As above.	0	Followed guidance.

	Impact on govt. health priorities	Overarching govt. priorities are child wellbeing, mental wellbeing, prevention, health equity, primary health care, with specific focus on rare diseases, cancer, long-term conditions, and infectious diseases. This does not enter the CUA.	SMA long-term condition.	0	Followed guidance.
Benefit	**Health benefit to the person**	What would be the health benefits or losses to the person who would receive the medicine? Looking at the net benefits over and above what is achieved by current treatments, including extension of life as well as improved HRQOL. As well as health benefits, **potential losses as a result of the funding decision should be considered. This includes harm done by adverse effects as well as no longer providing a gain that current treatment delivered.** Enters the CUA directly.	NURTURE trial discussed in the TAR. Interim level confidence from PTAC pending publication of final results. Considerable benefits to be gained through HRQOL with treatment. In the CUA. Adverse effects, however, not captured within the CUA.	2	Adverse events significant, and the risk particularly high with lifelong treatment assumed. Worth capturing or exploring to see if the risks and associated costs are negligible or not.
	Health benefit to the family, whanau, and wider society	What would be the health benefits for the family, whanau, or wider society of the person receiving treatment? Only clinically significant health benefits should be counted here - judgement required as to what is clinically significant. Benefits to others not usually counted in CUA, unless vaccines and herd immunity.	Likely reduction in caregiver burden, given interim data shows patients living longer and in better health. Not in CUA.	0	Followed guidance.
	Consequences for the health system	If the proposal was funded, what would be the consequences for the health system? Does it relate to any govt. priorities? Includes relieving or increasing pressure on the health system. **Flow-on effects may be complicated and their perceived presence should be justified or made clear that they are hypothetical.** Generally not included in CUA.	Considerable decrease in health system utilisation resulting from the high morbidity associated with SMA II patients. Delays in admissions etc. for SMA I patients too. Not in CUA.	0	Followed guidance.
Costs and savings	**To the person**	What would the health-related costs and savings be to the person who would be treated? Regardless of whether the patient pays it or it is subsidised by Vote Health. Change in costs and savings over status quo. May include GP visits, dispensing fees, travel costs, co-payments, part charges, care in home, etc. CUA generally only analyses costs that the govt. partially subsidises through the health sector budget. Private costs and savings are excluded from CUA.	None recognised. May be private savings from less healthcare requirements (travel etc.) but not considered in CUA, and not considered within dossier. Not in CUA.	0	Followed guidance.
	To the family, whanau, and wider society	Defined and considered in the same way as to the individual. Do not consider whether a family is privately funding a treatment for a patient, and any loss of income from inability to work is not included (however, consider inability to work as a loss of usual activities in the Need quadrant, and ability to work as a gain in usual activities in health benefit). Only certain direct healthcare costs are included in CUA, specifically those that the govt. partially subsidise through the health sector budget. Otherwise, costs and savings to family, whanau, and wider society are excluded from CUA.	Likely to reduce the level of care and costs associated with raising children with SMA. Potentially significant, but not quantified (magnitude not shown). Not in CUA.	1	Chance for further exploration given potential for significantly lower utilisation of public health services, as well as lower care burden.
	To pharmaceutical expenditure	How would funding the proposal impact pharma expenditure? Would fund it result in savings from switching from already funded pharmaceuticals? Net effect. Covers Combined Pharmaceutical Budget (CPB) and both hospital medicines and devices. Enters CUA.	Recognised and included in CUA.	0	Followed guidance.

	To the rest of the health system	Potential costs and savings that funding the proposal may have for the rest of the health system. Net effect. Not to be confused with health benefit consequences for the system. Defines health system as being Vote Health funding where that funding is enabling the delivery of health services. Includes DHBs, and any other services which are funded via Vote Health. Enters CUA.	Detection of pre-symptomatic SMA was assumed to occur through an additional test being added onto the current newborn heel prick testing. Insufficient consideration was given to the costs of establishing a new screening programme for SMA. The pre-symptomatic model also includes optimistic assumptions about the potential benefits of such a programme by assuming that those who initially respond to nusinersen have no loss of motor function over their lifetimes (lifetime utility of 0.91), and cases continue with lifetime treatment even in the absence of any symptoms. In practice this equates to around 245 intrathecal infusions per case over 80 years. We note there were no sensitivity analyses presented exploring the impacts of alternative scenarios of treatment completion, including cessation of treatment, on modelled costs or QALYs gained.	2	Analysis required to determine whether it is reasonable to assume there is the capacity and capability to add an SMA screening test on top of current screening tests. Also, necessary for consideration about the lifetime of treatment and the costs associated with that.
Suitability	**Features of the medicine that impact on use by the person**	What features may impact use by the person receiving the medicine? Is it registered for the disease or disorder that funding is being sought for? Includes issues that may make use difficult, less effective, or dissuade or prevent people from using it altogether. Can include size, shape, taste, method of delivery, ease of use, time required, packaging, supporting info, training. Subgroups particularly important to consider. **While this is likely to be reported with qualitative data, evidence is still required. If possible, compare with the suitability of existing treatments to show the size of the improvement or worsening.** Can affect a CUA result, but indirectly. **If significant enough to impact health benefits, will be included in CUA. Common example is when cost-effectiveness depends on the assumptions made about adherence and the costs and benefits and likelihood of an adherence programme affect use.**	None of the models included any complications from lifetime 4 monthly intrathecal infusions of Nusinersen. The clinical trials sourced in the PHARMAC modelling showed a high rate of adverse events (AE) in both the intervention and control (Sham injection) groups for symptomatic infants and children (Finkel et al. 2017; Mercuri et al. 2018). A number AEs were related to SMA making it difficult to distinguish between AEs associated with SMA, the medicine (nusinersen) or complications from intrathecal infusion. Complications of lumbar puncture were noted to be higher in the treatment group than control group in the child onset study (Mercuri et al. 2018). The time frames of the trials were limited to only a few years and additional risks may be expected from repeated infusions (4 monthly for life). Not considered or in the CUA.	2	Important to consider the adverse effects, given significance and frequency of treatment over lifetime.
	Features that impact on use by family, whanau, and wider society	Are there certain features of the medicine which could impact on health outcomes if it has to be given by someone other than the patient? Same as above about entering CUA.	Potentially increased travel and accommodation costs for carers etc. if there is travel requirement given capability for intrathecal injections may be limited to certain areas.	1	Analysis of national capability to provide intrathecal services would help.
	Features that impact on use by health workforce	Considering instances where members of the health workforce administer a medicine or medical device to a person. Considers how easy it is for a health worker to use, how likely it is a health worker could make an error. Could even include features which dissuade workers from using a product at all even though it could be clinically beneficial. Indirectly affects CUA.	Only able to be administered by people who can do intrathecal injection. Mentioned, but not well explored about what this could mean in terms of capacity.	1	As above.

Comparison of pembrolizumab against the Pharmac Factors For Consideration (FFC) Internal Guidance Document

Effectively, this acts as an audit of the different medicines against the Pharmac FFC Internal Guidance Document to assess deviations from recommended methodology. It also allows us to rank from 0 - 3 on a scale of severity of "error" (0 where it is adequate, 1 being a deviation but not likely to have made a difference to the decision, 2 being a deviation that should be noted and may be material, and 3 being a deviation that is material and significant).

Section	Sub-section	Description	Pembrolizumab (lung cancer)	Score	Comments	Pembrolizumab (melanoma)	Score	Comments
Need	**Health need of the person**	How unwell is a person with the health condition compared with an individual in perfect health? All significant health effects, physical and mental, are relevant and are taken into account when estimating health need. This may include comorbidities. Important to note, health need of individuals is not included in the CUA undertaken by Pharmac. It is simply a measurement of the disease burden irrespective of treatments already available or proposed. Health need of populations are however included in BIA, **and sometimes in CUA**. Assumedly, this would enter CUA when there is recognition of significant differences in prevalence across different population groups.	Lung cancer recognised as a significant health issue for NZ. Health need score reported, 19 (severe). Does not provide a separate health need score for Māori, who have been recognised to have 2-4x higher prevalence of lung cancer. Health need score aggregated may understate the significant difference in need for Māori. Should and very well could be reflected in separate CUA for Māori, but is not. Pembrolizumab has been shown to provide clinical benefit in improved overall and progression-free survival regardless of PD-L1 level (including PD-L1 negative) (Paz Ares et al. 2018; Gandhi et al. 2018). However, within the TAR, as a method for reducing the fiscal burden of pembrolizumab, it was proposed to limited eligibility to those with high levels of PD-L1>50 (representing about 25-30% of the clinical trial populations) based upon some (but inconsistent) evidence of a greater survival benefit seen for this group in overall survival (Paz Ares et al. 2018; Herbst et al. 2016) and progression free survival (Gandhi et al. 2018).	3	Separate analyses for Māori, given recognised disparities in prevalence, would be beneficial to ensure health need is well captured and expressed in the findings.	Health need described in dossier. PTAC/CaTSoP low priority recommendations. 7x higher incidence of melanoma in non-Māori than Māori, however Māori more likely to get advanced disease.	2	Discussion about the clear differences in prevalence/incidence would be beneficial. Not finding out how material this is, and what it means for the decision.
	Availability and suitability of existing medicines, medical devices, and treatments	What options are currently publicly funded to treat the population with this condition? How well do they work? A medicine is generally considered available if it is listed on the Schedule for the relevant indication. Consideration of the practicality, effectiveness, appropriateness of the treatment in the population group is necessary. this does come into the CUA because the CUA compares the proposal with current practice. The CUA focuses on net incremental benefit, however, so may not capture all the details of current treatment described under the Health Need Factor.	Current treatments outlined in the TAR. In order to make any assessment of whether pembrolizumab is likely to improve the vast disparities in lung cancer outcomes for Māori, it is critical to understand whether Māori would have equity in eligibility for this treatment. Within the provided documents, there is no estimate of the number of Māori with metastatic NSCLC (EGRF and ALK negative) with and without the criterion of PB-L1>50, that might be eligible for pembrolizumab under the proposed funding criteria. Therefore, while addressing an area of focus and high priority for Māori, we are unable to assess whether this treatment will provide equitable benefits for Māori.	3	Understanding of eligibility and current access barriers required.	Alternatives for unresectable and metastatic melanoma discussed in prioritisation dossier.	0	Followed guidance.
	Health need of the family, whanau, and wider society	What are the health needs for the family, whanau of the person with the disease, and the health needs for wider society? Considers the effect of a person's illness on the health of those around them. CUA may in some cases take into account the health need of others.	Carer burden for caring for people with cancer "well documented" elsewhere, as stated in the prioritisation dossier. Not in the CUA.	1	Assumed to be well documented elsewhere, but not included in documents received.	Not discussed in the documents.	1	Could be explored through literature on the burden of cancer on carers etc.
	Impact on Māori health areas of focus and Māori health outcomes	Has the disease, condition, or illness been identified as a Māori health area of focus? What is the impact on Māori health outcomes? This considers the diseases outlined in the Te Whaioranga 2013 - 2023: Māori Responsiveness Strategy. Areas are diabetes and renal disease, respiratory disease (asthma, COPD, lung disease), heart/cardiovascular, mental health, arthritis and gout, obesity, rheumatic fever. In general this doesn't enter CUA estimates. However, the guidance states that a CUA can be undertaken for different sub-groups, particularly where value for money for a population group experiencing a disparity is likely to be significant.	The modelling drew on international trial data for the starting proportions of the population on different treatment regimes, and transitions to: further treatments, supportive care and death. In addition, the main outcomes of overall survival and progression free survival for both the intervention arm (pembrolizumab) and the comparator arms of usual care come from trial data. There was no discussion provided on the relevance of these estimates in the New Zealand healthcare context for the New Zealand population, or for Māori specifically. New Zealand lung cancer survival rates are worse than a number of countries with comparable health systems (Lawrenson et al. 2018, Coleman et al. 2011). In addition, there are known disparities in lung cancer survival for Māori overall, by stage, and of particular relevance to pembrolizumab, Māori with distant disease are 30% more likely to die than non-Māori (with the same stage), HR 1.298 (95%CI 1.226- 1.374) (Gurney et al. 2020). The worse survival in New Zealand, and for Māori, means that there is the potential for pembrolizumab to achieve even greater benefits at the population level than demonstrated in clinical trials. The assumptions around cancer survival in the model are important as sensitivity analyses indicated that the models were most sensitive to assumptions around overall survival and the cost of pembrolizumab. The suggestion to restrict funding to PD-L1>50% is made without any information on the distribution of PD –L1 levels in Māori to ensure that such a requirement does not inequitably impact on access to this medication for Māori. Within the TAR it is acknowledged that PD-L1 testing is an invasive procedure (requiring a tissue sample) and may be variably used by clinicians (estimated at 10%) if not required as a part of the special authority. There is no consideration of the impact of known inequities in access to and quality of healthcare for lung cancer for Māori (Stevens et al. 2008; Te Aho o Te Kahu. 2021), on the likely rates of PD-L1 testing, and subsequent eligibility for pembrolizumab under this proposal.	3	Exploration absolutely necessary for Māori population who differ significantly from the trial population and have recognised disparities in health outcomes because of lung cancer. Separate CUA should have been undertaken.	Recognised in the dossier that the age standardised incidence rate of melanoma (no mention of late stage) is approx. 7x higher in non-Māori than in Māori, however like with most other cancers, Māori have significantly higher risk of being diagnosed with more advanced disease.	2	Discussion about the clear differences in prevalence/incidence would be beneficial.
	Impact on the health outcomes of population groups experiencing health disparities	What is the impact of the disease/condition on other population groups already experiencing disparities? To what extent does the disease disproportionately affect population groups that have substantive health disparities? This includes Pacific peoples, refugees, LGBTQI+, NZ deprivation deciles 9-10, sub-regionally deprived communities. The illness/disease/condition itself is not a sufficient way to define a group. **Guidance states that a CUA can be undertaken for different sub-groups, particularly where value for money for a population group experiencing a disparity is likely to be significant.**	The prioritisation dossier noted the major inequities in lung cancer registrations and deaths between Māori compared to non-Māori. However, no information on the epidemiology of the relevant types of lung cancer indicated for pembrolizumab is provided by ethnicity or considered for inequities, namely NSCLC (squamous and non-squamous). The PHARMAC TAR notes that NSCLCs comprise most (80%) of all lung cancers. This data is unreferenced. NZ data for 2015-2018 show that NSCLC comprise 70% of all lung cancers (Te Aho o Te Kahu. 2021), and this is slightly lower for Māori at 66%. In addition, PHARMAC documentation fails to provide context in relation to access to care. For example, PHARMAC have previously noted that access to treatments for cancers for Māori is a particular area of concern, with Māori 35% less likely to receive medicines for the treatment of cancers than non-Māori (adjusted for age and disease burden) (Metcalf et al. 2018). Relevant to this, the modelling does not consider the potential to optimise equity within existing treatment options or the impact of inequities in first line treatments when modelling pembrolizumab as a second line treatment.	3	See above.	Recognised in the dossier that the age standardised incidence rate of melanoma (no mention of late stage) is approx. 7x higher in non-Māori than in Māori, however like with most other cancers, Māori have significantly higher risk of being diagnosed with more advanced disease.	2	Discussion about the clear differences in prevalence/incidence would be beneficial.
	Impact on govt. health priorities	Overarching govt. priorities are child wellbeing, mental wellbeing, prevention, health equity, primary health care, with specific focus on rare diseases, cancer, long-term conditions, and infectious diseases. This does not enter the CUA.	Identified as govt. priority area with cancer. No benefits identified for govt. priorities, however.	1	Should be recognised that lung cancer inequitably affects Māori and Pacific peoples, and therefore the benefits of treating lung cancer go to the govt. priority of equitable health care.	Cancer.	0	Followed guidance.
Benefit	**Health benefit to the person**	What would be the health benefits or losses to the person who would receive the medicine? Looking at the net benefits over and above what is achieved by current treatments, including extension of life as well as improved HRQOL. As well as health benefits, **potential losses as a result of the funding decision should be considered. This includes harm done by adverse effects as well as no longer providing a gain that current treatment delivered.** Enters the CUA directly.	Adverse events (including those categorised as serious and severe) were common in the clinical trials for both the intervention (pembrolizumab) and comparator groups (Paz Ares et al. 2018; Gandhi et al. 2018; Reck et al. 2016). For example, in the Paz Ares 2018 clinical trial of combination first line therapy, 69.8% and 68.2% of patients in the intervention and comparator groups respectively experienced severe adverse events. Adverse events from pembrolizumab were not included in the base models. Sensitivity analyses were run to examine the additional costs of adverse events, but there was no consideration of the health impacts or (disutility) of experiencing an adverse event.	1	Not well considered - benefits from exploring the significance of adverse events on HRQOL.	The analysis of pembrolizumab was indirect since there were no trials comparing pembrolizumab to the active treatment (dacarbazine) in the treatment naïve unresectable or metastatic melanoma population. The appropriateness and implications of this indirect analysis do not seem to have been discussed in depth within the documents provided by Pharmac. The economic Markov model was informed from a clinical trial (Schachter et al. ,2015). It is not immediately clear from analysis whether this was appropriate, or demonstrably applicable to the New Zealand context. The Pharmac PFPA document recommends trials be critically appraised using the GATE framework. It is not clear that this was undertaken. In the CUA as expected.	1	Despite there being no direct comparison trials at the time, discussion around the appropriateness of the indirect comparison and the implications would be beneficial.
	Health benefit to the family, whanau, and wider society	What would be the health benefits for the family, whanau, or wider society of the person receiving treatment? Only clinically significant health benefits should be counted here - judgement required as to what is clinically significant. Benefits to others not usually counted in CUA, unless vaccines and herd immunity.	None identified in documents.	0	Followed guidance.	Not discussed within the documents. One could assume there would be benefits from longer life expectancy.	1	Beneficial inclusion to frame the context of the treatment and what it means for family, whanau, society.
	Consequences for the health system	If the proposal was funded, what would be the consequences for the health system? Does it relate to any govt. priorities? Includes relieving or increasing pressure on the health system. **Flow-on effects may be complicated and their perceived presence should be justified or made clear that they are hypothetical.** Generally not included in CUA.	None identified in documents.	0	Followed guidance.	Pharmac expressed uncertainty around the current oncology infusion capacity of DHBs for the number of patients expected to receive pembrolizumab treatment. The analysis conducted by Pharmac assumed there would be the capacity to meet the extra demand for oncology infusion services, however this did not seem to be a well tested assumption throughout the analysis (i.e. is it feasible for DHBs to increase their infusion capacity?). The implications of funding a medicine without having the capacity to administer it have not been well captured. The potential disbenefits also of closing out other infusion treatments for other diseases are not well captured either. Recommendation was made by PTAC and CaTSoP in late 2015 to fund pembrolizumab on low priority, funding recommendation made in mid-2016 by board for pembrolizumab as an additional treatment for late-stage melanoma. Recommendation for low priority only seemingly on the basis of an early evidence base and uncertainty about the medicine's longer term benefits, as well as potential risks and very high cost. No consideration about DHB capacity, and unclear whether the decision to fund the medicine was influenced at all by the fact this is not a high priority area for Māori.	3	Analysis of the feasibility and likelihood of infusion capacity increasing is very important, given recognised capacity constraints and therefore the potential for pembrolizumab administration to close out other infusion treatments (i.e. disbenefits to other people and system).
Costs and savings	**To the person**	What would the health-related costs and savings be to the person who would be treated? Regardless of whether the patient pays it or it is subsidised by Vote Health. Change in costs and savings over status quo. May include GP visits, dispensing fees, travel costs, co-payments, part charges, care in home, etc. CUA generally only analyses costs that the govt. partially subsidises through the health sector budget. Private costs and savings are excluded from CUA.	None identified.	0	Followed guidance.	None noted by Pharmac.	0	Followed guidance.

	To the family, whanau, and wider society	Defined and considered in the same way as to the individual. Do not consider whether a family is privately funding a treatment for a patient, and any loss of income from inability to work is not included (however, consider inability to work as a loss of usual activities in the Need quadrant, and ability to work as a gain in usual activities in health benefit). Only certain direct healthcare costs are included in CUA, specifically those that the govt. partially subsidise through the health sector budget. Otherwise, costs and savings to family, whanau, and wider society are excluded from CUA.	None identified.	0	Followed guidance.	Not mentioned.	0	Followed guidance.
	To pharmaceutical expenditure	How would funding the proposal impact pharma expenditure? Would fund it result in savings from switching from already funded pharmaceuticals? Net effect. Covers Combined Pharmaceutical Budget (CPB) and both hospital medicines and devices. Enters CUA.	Recognised in documents. In CUA.	0	Followed guidance.	Measured in the BIA.	0	Followed guidance.
	To the rest of the health system	Potential costs and savings that funding the proposal may have for the rest of the health system. Net effect. Not to be confused with health benefit consequences for the system. Defines health system as being Vote Health funding where that funding is enabling the delivery of health services. Includes DHBs, and any other services which are funded via Vote Health. Enters CUA.	Additional costs for infusion hours. In the CUA.	0	Followed guidance.	Measured in the BIA.	0	Followed guidance.
Suitability	**Features of the medicine that impact on use by the person**	What features may impact use by the person receiving the medicine? Is it registered for the disease or disorder that funding is being sought for? Includes issues that may make use difficult, less effective, or dissuade or prevent people from using it altogether. Can include size, shape, taste, method of delivery, ease of use, time required, packaging, supporting info, training. Subgroups particularly important to consider. **While this is likely to be reported with qualitative data, evidence is still required. If possible, compare with the suitability of existing treatments to show the size of the improvement or worsening.** Can affect a CUA result, but indirectly. **If significant enough to impact health benefits, will be included in CUA. Common example is when cost-effectiveness depends on the assumptions made about adherence and the costs and benefits and likelihood of an adherence programme affect use.**	The clinical trial populations differed in important ways to the Māori population, for example the clinical trial participants were mostly male (59-81%) (Gandhi et al. 2018; Herbst et al. 2016; Paz Ares et al. 2018; Reck et al. 2016) whereas 56% of all lung cancers in Māori are in Māori females (Ministry of Health. 2018). In addition, Māori are diagnosed with lung cancer at a younger median age than non-Māori (Lawrenson et al. 2018; Te Aho o Te Kahu). The impacts of these differences were not considered in the CUA or supporting documentation. Unclear how pembrolizumab will work for Māori. Shorter treatment term recognised as a benefit for the person.	3	Exploration absolutely necessary for Māori population who differ significantly from the trial population and have recognised disparities in health outcomes because of lung cancer. At the very least, comments required abut the suitability of the treatment for Māori population.	Not discussed in detail.	1	Brief discussion of any differences between current treatment and proposed treatment would be beneficial (e.g. infusion time, side effects that differ, etc.)
	Features that impact on use by family, whanau, and wider society	Are there certain features of the medicine which could impact on health outcomes if it has to be given by someone other than the patient? Same as above about entering CUA.	None identified.	0	Followed guidance.	Not discussed.	0	Followed guidance.
	Features that impact on use by health workforce	Considering instances where members of the health workforce administer a medicine or medical device to a person. Considers how easy it is for a health worker to use, how likely it is a health worker could make an error. Could even include features which dissuade workers from using a product at all even though it could be clinically beneficial. Indirectly affects CUA.	None identified, however may have implications for infusion capacity.	1	Important to look at infusion capacity to understand the impact different treatments may have on the health workforce.	Assumption that there will be an increase in oncology infusion capacity. May put pressure on existing capacity and close out other treatments.	3	Analysis of the feasibility and likelihood of infusion capacity increasing is very important, given recognised capacity constraints and therefore the potential for pembrolizumab administration to close out other infusion treatments (i.e. disbenefits to other people and system).

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