Review of PHARMAC cost-utility analysis modelling approaches in relation to Māori health equity

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The objectives of our review were to provide a Māori health equity-based peer review of PHARMAC CUA modelling to:

- Consider how the PHARMAC medicine assessments have taken into account and reflect matters relating to equity
- Identify if there are any omissions of information that you consider to be a serious gap in PHARMAC's analysis
- Provide recommendations on how Māori health equity in PHARMAC CUA modelling may be strengthened.

This was based on the review of a series of case studies using:

- Empaglifozin
- Nusinersen
- Pembrolizumab
- Ustikinumab
- Venlafaxine

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Contents

Summary of findings across case studies 3
Recommendations for PHARMAC cost-utility analyses 6
Recommendations for Māori health equity in CUA modelling 6
General recommendations on the modelling approach 8
Brief review of PHARMAC CUA analysis of empagliflozin for type 2 diabetes with established high cardiovascular disease risk 10
Brief review of PHARMAC CUA analyses of nusinersen for Spinal Muscular Atrophy (types I, II and IIIb) 14
Brief review of PHARMAC CUA analysis of pembrolizumab for metastatic non-small cell Lung Cancer 17
Brief review of PHARMAC CUA analysis of ustekinumab for moderate to severe Crohn's disease 21
Brief review of PHARMAC analysis of venlafaxine (brand switch) for depression and anxiety 25

Summary of findings across case studies

In reviewing the case studies and cost-utility analyses (CUAs), there was a concerning absence of information on Māori health needs and inequities and a lack of any connection to other assessment areas. The lack of a systematic approach to identify, account for, and address known (or potential) underdiagnoses and under treatment of Māori in the current healthcare system normalises and further perpetuates these inequities and is an expression of systemic racism.

Despite PHARMAC clearly articulating a commitment to Te Tiriti o Waitangi and towards achieving the best health outcomes for Māori in Te Rautaki o te Whaioranga - Māori Responsiveness Strategy (PHARMAC 2020), with identified priorities and goals, these were not reflected in the documentation of case studies we reviewed. There was no consideration of Māori health and equity within the CUA models themselves (discussed further below) and very superficial consideration of Māori health and equity in the documentation surrounding the CUA models. This was confined to the prioritization dossier 'need' section and background sections of TARs. The restriction of Māori health commentary to the 'need' section of the factors for consideration (FFC) is problematic as it serves to limit consideration of Māori health to one area when it has relevance to all assessment areas including CUA modelling and budget impact assessment (BIA).

The scope of information regarding Māori health and inequities in the background documentation was very limited and did not provide adequate context with which to inform CUA approaches, interpretation, or wider assessment areas. Where inequities were considered, this was at a high level (e.g. inequities in lung cancer) rather than for the specific treatment indication (e.g. non-small cell EGFR wildtype lung cancer). The longstanding systemic inequities in health outcomes, and access to and quality of care for Māori across many health areas dictates that the consideration of medicines should be situated within this broader context. This level of information was not provided in the supporting documentation for specific medicines and relevant health issues. There was little to no consideration of unmet need and inequities in access to diagnosis and existing treatment options which limited Māori eligibility for medicines even though a useful resource has been developed and published by PHARMAC looking at inequities in access to medicines (Metcalf et al. 2018). The resulting impact is that existing inequities in access to medicines are implicitly accepted and systematically built into CUA models and BIAs.

Where areas of Māori health importance were noted (albeit briefly and at a high level), there was then no apparent connection or thought given to the relevance of that information to other areas of assessment including CUAs, BIAs and other FFC, even for areas of identified high Māori health need with known major inequities such as lung cancer, mental health and diabetes. The little evidence that was provided was merely stated and taken no further.

Three key issues were identified with the PHARMAC cost-utility analysis approach. The first issue relates to the lack of consideration of the impact of existing inequities in health and healthcare in the CUA models and BIA and the implicit assumption that all interventions are applied within existing models of healthcare. This issue partly arises from disconnect

between the CUA and with the other factors for consideration where Māori health need, inequities for Māori and areas of focus for Māori should have been identified. In addition, the measures of health need and BIAs (which includes an estimate of the eligible population) were not prepared separately for Māori despite offering a potentially useful way of assessing the appropriateness of proposed eligibility criteria.

Given the weak assessment of Māori health and inequities in the factors for consideration, PHARMAC should revisit their recommendation not to use equity weights for health-related quality of life to account for distributive justice and health need. *"HR-QoL weights used to calculate QALYS should not be adjusted or weighted for value judgements on issues such as distributive justice, respect for autonomy, or health need. PHARMAC's Factors for Consideration provide a framework to ensure that all relevant aspects and issues are taken into account in an overall decision"* (PHARMAC. Prescription for Pharmacoeconomic Analysis). Ideally PHARMAC would develop a robust systematic process for considering Māori health and health equity which would then be applied to CUA, BIA and measures of health need, and used in the decision-making process. In the absence of this systematic process, equity weights offer a crude way to adjust for issues of distributive justice and inequitable health need.

The second issue with the CUAs relates to the (uncritical) use of international data within the CUAs, even where New Zealand data are available. The PHARMAC document Prescription for Pharmacoeconomic Analysis (PFPA) identifies the target population of economic analyses as "*the New Zealand population most likely to receive treatment. Any differences between the population in the key clinical trials and the target population should be discussed in the report*"(PHARMAC. Prescription for Pharmacoeconomic Analysis). In practice, over the five case studies, PHARMAC instead modelled the cost-effectiveness of new medicines for the clinical trial/RCT populations within the trial health systems and applied some New Zealand costs. The only evidence of any attempts to model the New Zealand population in the five case studies we reviewed was through the inclusion of a New Zealand lifetable for background mortality in two of the four case studies that had CUA models, and by applying New Zealand healthcare costs (at times applied to resource use estimated from international data). All CUA models reviewed used data from international trials as the target population to populate the baseline proportions (e.g. the number of people in each starting health state) the transitions (or progressions) to other health states (e.g. progression to more advanced disease) and, for outcomes in both the intervention and comparator arms of the model. Of concern was the lack of validation and discussion about the relevance of trial data for the New Zealand population and specifically for the Māori population with a younger population age structure and differing patterns of disease and healthcare utilisation.

The third key issue is the lack of comparability across the CUA models; a key purpose of the CUA models. Despite presenting clear recommendations on a consistent approach to CUA modelling in the PFPA, there was wide variation across the models we reviewed in the source of utilities and the length of the modelled time horizons (most of 20 years duration, but ranging from 10-80 years). As discussed above, there was also wide variation in the clinical trial populations modelled and the healthcare systems they are drawn from.

References

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Recommendations for PHARMAC cost-utility analyses

The following recommendations are intended to guide the direction of PHARMAC equity considerations within CUAs. These recommendations are pitched around improving current methods and processes used by PHARMAC in their assessment of medicines, although many of the recommendations are likely applicable should there be a major shift in PHARMACs' approach. We do not present a prescriptive set of CUA modelling methods but rather a more flexible range of approaches to fit with varying availability and quality of data, and for priority conditions identified as "Māori health areas of focus". The incorporation of health equity into the CUAs and across PHARMAC activities depends upon having appropriate expertise within the organisation (including expertise in Māori health and health equity), in order to enable the safe application of these methods and interpretation of findings. The recommendations are presented in two groups; those that relate to incorporating Māori health equity, and more general recommendations on the modelling approach.

Recommendations for Māori health equity in CUA modelling

1. Set an organisational expectation that PHARMAC will contribute positively to the elimination of inequities in health for Māori, and follow through with that expectation

1.1 Implement Te Rautaki o te Whaioranga across all PHARMAC activities including CUAs.

> PHARMACs Te Tiriti o Waitangi goal and outcomes states that:
>
> *"PHARMAC honours and actively upholds Te Tiriti across all our work to achieve best health outcomes for Māori within our available resources.*
>
> *Te Tiriti is embedded and is fundamental to PHARMAC's objectives and working culture, and sits alongside PHARMAC's purpose.*
>
> *Te Tiriti is reflected in the way we plan for, resource, organise and deliver our work as an organisation, and we measure and monitor organisational Te Tiriti compliance.*
>
> *All our work delivers for Māori, with Māori, by Māori. This is planned for and appropriately resourced across all directorates."*
>
> Source: Te Rautaki o te Waioranga (Māori responsiveness strategy)
> https://pharmac.govt.nz/assets/Te-Whaioranga-August-2020.pdf

2. Build PHARMAC capacity for addressing health equity in CUA modelling

2.1 Develop the internal capacity of PHARMAC to identify, account for and address inequities in health for Māori both through upskilling of existing staff, and by adding in Māori health experts across a range of roles.

2.2 Enhance engagement with external Māori health experts (and value this expertise by resourcing it appropriately).

3. Develop a process for systematically assessing Māori health and equity to inform PHARMAC decision-making processes and CUAs

3.1 Consider Māori health and equity across all aspects of the PHARMAC decision-making process including across all FFC and in CUAs.

3.2 Develop a systematic approach to understanding the epidemiology of health issues for Māori. This should incorporate existing data on disease burden, inequities in outcomes, diagnosis and treatment, and should consider where distributions by specific indicators are important e.g. age, gender, stage, histological type etc. Where data is not available, health issues should be considered in the broader context of health and healthcare inequities for Māori.

3.3 Use this data to inform decision-making processes at the outset of any processes to change or consider new medicines and in the approaches to and interpretation of CUAs and BIAs.

4. Draw upon internal and external expertise, consider the following modelling methods to incorporate Māori health equity

4.1 Consider modelling separately for Māori where: the health issue is identified as a Māori health area of focus, where sufficient and high-quality data are available to populate baseline health states and the average starting population.

Modelling for population "subgroups" is consistent with the PFPA, however health equity should also be a key reason for this type of analysis.

"Analyses for population subgroups should be used if value for money can be improved by targeting funding to those who are most likely to benefit"

Source: PFPA

4.2 Use sensitivity analyses to explore the impact of differences in key parameters for Māori (baseline proportions, survival), and then use this information to help refine eligibility criteria, or as further evidence for the factors for consideration.

4.3 Reconsider weighting health-related quality of life for distributive justice (as a less useful but alternative method in the absence of a systematic approach to FFC and their incorporation in CUAs).

4.3 Model equitable access to current treatment options alongside new treatment options and rank and fund interventions accordingly.

4.4 Seek internal and external peer review of key assumptions, the modelling approach and inclusion of health equity.

4.5 Develop outputs to measure the impact of treatment options on inequities, and/or the distributions of health gains. This may be as a part of the CUA models outputs or in the BIA.

5. Avoid perpetuating inequities by assuming the current patterns of inequitable healthcare continue

5.1 Measure "health need" and Budget Impact Assessment (BIA) separately for Māori.

5.2 Use total population life expectancy when calculating "health need" for Māori to avoid setting an expectation for ongoing inequities in life expectancy.

5.3 Compare the Māori specific health need measure and the BIA (which captures the eligible population) to identify any mismatch between health needs and treatment eligibility.

5.4 Adjust eligibility criteria where inequities in access to healthcare unfairly restrict eligibility of Māori (e.g. access to a diagnosis, 1st or 2nd line treatment).

6. Contribute PHARMAC resource to addressing inequities in existing treatment options

6.1 Consistent monitoring of equity of access to new and existing medicines.

6.2 Respond where inequities are identified, for example consider adjustments to eligibility criteria, engaging and educating with healthcare providers, engagement with Māori communities and experts to identify and reduce barriers to medicine access.

General recommendations on the modelling approach

7. Engage critical analyses skills when using international data

7.1 Articulate the purpose of the CUA in model documentation– specifically, if the aim is to model the drug in the New Zealand or trial context.

7.2 Identify which data in the models are from New Zealand

7.3 Use New Zealand data (e.g. on baseline proportions, mortality) in the baseline models.

7.4 Develop a systematic approach for considering (and documenting) the relevance of international data to the New Zealand population and New Zealand healthcare system, and

7.5 Use sensitivity analyses to explore the impact of the New Zealand context (identified above) on modelled results.

8. Improve the comparability of the CUA models

8.1 Apply the approach outlined in the PHARMAC cost resource manual to estimate resource costs.

"Where feasible, resource use estimates should be based on New Zealand information from clinical guidelines, expert clinical opinion, clinical trials, and/or the Ministry of Health. If New Zealand data is not available, international sources may be used, but should be ***validated for the New Zealand setting***"

Source: https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/policies-manuals-and-processes/economic-analysis/cost-resource-manual/

8.2 Apply the recommended approach outlined in the PFPA for improving consistency in setting (and justifying) the model time horizon

"*In the majority of CUAs, a* ***lifetime horizon*** *should be used and half-cycle adjustment applied. However, for conditions that are unlikely to exist over a lifetime, or where there is uncertainty around whether survival benefits will persist, the choice of a shorter time horizon (eg until recovery or death) can be justified, providing there are no differences in mortality, long-term morbidity and cost between the alternative options. The report should always* ***justify the time horizon*** *used in the analysis."*

8.3 Apply the recommended approach outlined in the PFPA for improving consistency in health-related quality of life.

"The New Zealand EQ-5D Tariff 2 should be referred to first when measuring health-related quality of life, 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."

Brief review of PHARMAC CUA analysis of empagliflozin for type 2 diabetes with established high cardiovascular disease risk

Documents

For this review we were provided with:

1. The PHARMAC empagliflozin TreeAge model
2. TAR 382 _ SGLT 2 inhibitors for type 2 diabetes with established high cardiovascular disease (with redaction of cost outputs and other data and tables)
3. Prioritisation dossier SGLT inhibitors
4. *2021 06 03 combined reports briefing documents etc for release* attached at the bottom of this OIA response: https://pharmac.govt.nz/about/what-we-do/accountability-information/official-information-act/2021-oia-responses/3-june-2021-oia-response-decision-to-change-special-authority-criteria-for-empagliflozin-and-dulaglutide/
5. Q and A https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/decision-to-fund-two-new-medicines-for-type-2-diabetes/

This review focusses on documents 1-3.

Brief description of the model

A full description of the model is provided in TAR 382 _ SGLT 2 inhibitors for type 2 diabetes with established high cardiovascular disease risk. Key points on the model approach required as context for this review are provided here. The model is a simple Markov model built in TreeAge comparing empagliflozin to current best care for those with type 2 diabetes and high cardiovascular risk.

Intervention: SGLT-2 empagliflozin once daily tablet 10mg or 25mg	**Time horizon**: 10 years
Comparator: Current best care	**Perspective**: Funder
Outcomes: All-cause death, heart failure hospitalisation, progression to macroalbuminuria and initiation of renal replacement therapy, initiation of insulin	**Discounting**: 3.5% on costs and benefits

Did the CUAs consider and reflect matters relating to equity

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 drug 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.

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.

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.

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 (see table 1 for an extract of these data from the model). 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.

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.

Table 1 Input parameters from International RCT in PHARMAC empagliflozin model

Variable	Model variable name	Values (Zinman 2015; Wanner 2016)
Annual rate of all cause death placebo	rate_death_placebo	0.029
Annual rate of all cause death SGLT	rate_death_SGLT	0.019
Annual rate of heart failure hospitalisation placebo	rate_HFH_placebo	0.015
Annual rate of heart failure hospitalisation SGLT	rate_HFH_SGLT	0.009
Annual rate of progression to macroalbuminuria placebo	rate_macroalbum_placebo	0.0649
Annual rate of progression to macroalbuminuria SGLT	rate_macroalbum_SGLT	0.0418
Annual rate of initiating renal replacement therapy placebo	rate_RD_placebo	0.002
Annual rate of initiating renal replacement therapy SGLT	rate_RD_SGLT	0.001

Strengths and weaknesses of general modelling approach

Overall, the TAR provided a good overview of the model and key assumptions. The model itself included sensitivity analyses on discount rates, baseline proportions, clinical parameters, utilities, pharmaceutical costs, time horizons, and other costs. The model drew heavily on international data and lacked appropriate critique of the relevance of these data in the New Zealand context.

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.

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.

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.

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.

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Ministry of Health. Ngā mana hauora tūtohu: Health status indicators: Diabetes. Available at: https://www.health.govt.nz/our-work/populations/Māori-health/tatau-kahukura-Māori-health-statistics/nga-mana-hauora-tutohu-health-status-indicators/diabetes

Brief review of PHARMAC CUA analyses of nusinersen for Spinal Muscular Atrophy (types I, II and IIIb)

Documents

For this review we were provided with:

- The PHARMAC nusinersen CUA model in Excel
- TAR 398 – Nusinersen for Spinal Muscular Atrophy (with redaction)
- Prioritisation dossier for nusinersen

Brief description of the model

A full description of the model is provided in TAR 398 – nusinersen for Spinal Muscular Atrophy. Key points on the model approach required as context for this review are provided here.

Three separate CUA models were undertaken for the use of nusinersen for the following indications:

1. Symptomatic SMA (types I, II, IIIa): combined two models for symptomatic treatment of infantile (SMA type I) and childhood onset (SMA type II and IIIa) SMA
2. Pre-symptomatic individuals with SMA
3. Combined pre-symptomatic and symptomatic SMA (types I, II, IIIa)

Intervention: Intrathecal nusinersen 12mg Loading dose at day 0, 12, 28 and 63 Maintenance dose 4 monthly	**Time horizon**: Symptomatic 10 years, pre-symptomatic 80 years
Comparator: Supportive care	**Perspective**: Funder
Outcomes: Overall survival (with no ventilation assistance) WHO motor milestone achievement	**Discounting**: 3.5% on costs and benefits

Did the CUAs consider and reflect matters relating to equity

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. 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.

Within the prioritisation dossier, "Māori health areas of focus" and "Māori health need" were noted as "not applicable".

Strengths and weaknesses of general modelling approach

Overall the TAR provided a good overview of the model and key assumptions. 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). Given the lack

of New Zealand data on SMA 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. 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. 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.

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)(Table 1). 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).

Table 1 Direct medical and direct non-medical* costs by SMA types used in infantile onset and childhood SMA models

Cost	Supplier	PHARMAC	Rationale
SMA type I (annual COI)	$91,302	$99,749	Supplier estimate is in $AUS. PHARMAC have converted the original € estimate into $NZD with adjustment for inflation.
SMA type II (annual COI)	$26,019	$28,329	Supplier estimate is in $AUS. PHARMAC have converted the original € estimate into $NZD with adjustment for inflation.
SMA type III (annual COI)	$15,513	$16,812	Supplier estimate is in $AUS. PHARMAC have converted the original € estimate into $NZD with adjustment for inflation.

Source: TAR 398 – Nusinersen for Spinal Muscular Atrophy (with redaction), pg 38
*Direct non-medical costs including expenses relating to housing, travel, informal care costs, modifications to house and automobile.

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 drug (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).

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.

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.

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.

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Brief review of PHARMAC CUA analysis of pembrolizumab for metastatic non-small cell Lung Cancer

Documents

For this review we were provided with:

- The PHARMAC 2021 Lung 1L model 5.0 and 2021 Lung 2L model 5.0
- TAR 436 –ICI for metastatic NSCLC 1L and 2L (multiple proposals)
- Prioritisation dossier for pembrolizumab

Brief description of the model

Full descriptions of the models are provided in TAR 436 –ICI for metastatic NSCLC 1L and 2L (multiple proposals). Key points on the model approach required as context for this review are provided here.

Two separate CUA models were undertaken for the use of pembrolizumab for EGFR wildtype (aka EGFR negative) metastatic NSCLC for the following indications (and combinations of):

2. 1st line monotherapy PD-L1 expression >50%
3. 1st line combination therapy
4. 2nd line monotherapy

Intervention: IV infusion pembrolizumab 200mg 3 weekly or 400mg 6 weekly (for up to 2 years as second line treatment)	**Time horizon**: 20 years for both 1st and 2nd line models
Comparator: Current practice 1st line Platinum based chemotherapy 2nd line docetaxel	**Perspective**: Funder
Outcomes: Overall survival Progression of disease	**Discounting**: 3.5% on costs and benefits

Did the CUAs consider and reflect matters relating to equity

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.

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.

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.

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 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.

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.

Strengths and weaknesses of general modelling approach

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.

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.

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 drug treatments to estimate current care and applied NZ drug 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.

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Brief review of PHARMAC CUA analysis of ustekinumab for moderate to severe Crohn's disease

Documents

For this review we were provided with:

- The PHARMAC Inflammatory Bowel Disease (IBD) core model 2.0 – with redactions
- TAR 372 – Ustekinumab for Crohn's disease
- Prioritisation dossier ustekinumab for Crohn's redacted copy

Brief description of the model

A full description of the model is provided in TAR 372 – Ustekinumab for Crohn's disease. Key points on the model approach required as context for this review are provided here.

Ustekinumab was modelled through an existing TreeAge IBD model that had previously been used to assess drugs for Crohn's and Ulcerative colitis. Two separate scenarios were modelled for moderate to severe Crohn's disease for the following indications:

1. As second line therapy (after infliximab)
2. As a third line therapy (after infliximab and adalimumab)

Intervention: Ustekinumab 390mg IV loading on day 1, then 90mg SC maintenance every 8 weeks.	**Time horizon**: 20 years
Comparator: Placebo and current standard of care (based on clinical trial comparator)	**Perspective**: Funder
Outcomes: Primary outcome: reduction in Crohn's Disease Activity Index (CDAI) score informing non-response, response (a decrease from baseline in of ≥100 points or a CDAI score <150), partial response and remission (CDAI score < 150)	**Discounting**: 3.5% on costs and benefits

Did the CUAs consider and reflect matters relating to equity

The CUA models did not account for health equity in their structure, data inputs or outputs. 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. 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.

Strengths and weaknesses of general modelling approach

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. By using this consistent model structure, there is improved consistency in the modelling of drugs 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.

The ustekinumab modelling drew on clinical trial data up to 92 weeks (1 year and 11 month), with a model time horizon of 20 years justified based on limited follow-up time. Based upon clinical trial data, the model included a large primary non-response (62% non-response at 8 weeks) and further loss of response at 52 weeks (40.6% of those that were responding at 8 weeks). Secondary loss of response of 14% per annum was applied for the remainder of the 20-year time horizon based upon the "long-term extension study" of ustekinumab efficacy that went up to 92 week (less than 2 years) (Sandborn et al, 2018). 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).

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).

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.

Table 1 Health system costs by health state (annual)

Item	Item cost source	Item cost	Remission	Response	Non-response	Post-surgery (no major complications)	Post-surgery (major complications)
Inpatient	WEISNZ13	$4,325.98	0	0	1	0	1
ED	Cost Manual	$680.00	0	0	1.5	0	1.25
Specialist	Cost Manual	$150.00	2	2.25	6.5	4	8
GP	Cost Manual	$80.00	1.625	1.625	5	2	6
Blood test	Cost Manual	$15.00	2.75	3.25	9.75	5	10.25
Imaging	Auckland X-Ray	$299.10	0	0.25	1.625	0.75	1.875
Endoscopy	Cost Manual	$843.36	0.125	0.5	2	0.5	0.625
Colonoscopy	NMPAC	$943.34	0	0	1	0	0
Average cost			$576.67	$1,012.71	$9,983.34	$1,481.01	$8,097.65

The clinical trial did not examine intervention efficacy by age or gender, so it was appropriate not to examine this in the base model (Feagan et al. 2016).

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.

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Brief review of PHARMAC analysis of venlafaxine (brand switch) for depression and anxiety

Documents
For this review we were provided with:

- PHARMAC Board papers for 30 September 2016 – Recommendation to award sole supply of venlafaxine in the community and DHB hospitals
- Additional appendices to the board papers

Brief description of the recommendation for a brand switch
This case study reviewed the recommendation and rationale to award Sole Subsidised Supply Status and Hospital Supply Status to the supplier Mylan for venlafaxine (Enlafax XR) following an invitation for tenders in June 2016.

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRIs) indicated for the treatment of major depression; generalised anxiety disorder; social anxiety disorder and panic disorder. It is also indicated for the prevention of relapse and recurrence of major depression.

Intervention (recommended venlafaxine brand): Enlafax XR, Mylan (35.7mg, 75mg, 150mg capsules) without restriction	**Assumptions:** Bioequivalence between venlafaxine brands
Comparator (previously subsided venlafaxine brands): Arrow-Venlafaxine, Actavis (37.5mg, 75mg, 150mg, 225mg tablets) without restriction Efexor XR, Pfizer (37.5mg, 75mg, 150mg capsules) on Special Authority	**Cost savings (from brand switch):** Approx. $18.4 million to the Combined Pharmaceutical Budget (CPB) and $20.5 million to DHBs overall including hospital savings (5-year NPV, 8% discount rate).
Outcomes/indications: Enlafax XR is registered for same indications as other brands.	**Current venlafaxine use:** Approx. 45,000 people in New Zealand on venlafaxine among whom: 73% were receiving it for chronic illness (>4 months); 8% were Māori and Pacific, 68% were on Efexor; and 700 were being dispensed 225mg tablets (long term) that were to be delisted.

No formal CUA analysis was undertaken for the brand switch recommendation. Bioequivalence of Enlafax was assumed with previously subsidised brands registered for the same indications. Reduced price was the sole change and therefore, cost-effectiveness was assumed to be "improved substantially." The removal of special authority and introduction of stat dispensing may impact on access to venlafaxine but was not assessed.

Did the brand change consider and reflect matters relating to Māori health and equity?

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.

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.

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.

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