PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 20 & 21 February 2020

The records of PTAC and Subcommittees of PTAC are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the meeting; only the relevant portions of the record relating to discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

PTAC and Subcommittees of PTAC may:

a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

Present:

PTAC members:
Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Bruce King
Giles Newton Howes
Jane Thomas
Matthew Strother
Simon Wynn Thomas
Stephen Munn
Tim Stokes

Apologies
Jennifer Martin
Sean Hanna

1. The role of PTAC, PTAC Subcommittees and meeting records

1.1. This meeting record of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

1.2. The PTAC Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC and PTAC Subcommittees.

1.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

1.4. PTAC and PTAC Subcommittees have complementary roles, expertise, experience, and perspectives:

- Both PTAC and PTAC Subcommittees are statutory advisory committees established by the PHARMAC Board (external to and separate from PHARMAC staff). Both provide objective advice to PHARMAC on community and hospital pharmaceuticals and their benefits, using the PHARMAC Factors for Consideration.

- PTAC considers Applications or PHARMAC staff proposals across all therapeutic groups in the Pharmaceutical Schedule. It has an overview view of Applications and other items referred to it for clinical advice. PTAC provides and promotes critical appraisal of strength and quality of evidence, applied rigorously, systematically and consistently across all therapeutic groups.

- PTAC Subcommittees provide objective advice within specific therapeutic areas. PTAC Subcommittees are separate from, and not subordinate to, PTAC. PTAC Subcommittees are appointed to reflect specialist knowledge and expertise in health needs and treatments within their own therapeutic groups/areas of clinical practice, including the applicability of evidence to clinical funding settings in New Zealand. PTAC Subcommittees make recommendations, including providing a priority, within their therapeutic groups of interest.

- PTAC and PTAC Subcommittees therefore provide separate and different, if complementary, perspectives and advice to PHARMAC. PTAC examines the same evidence with a different perspective from specialist expert PTAC Subcommittees, as do Subcommittees between them.

1.5. PTAC may therefore, at times, make recommendations that differ from PTAC Subcommittees', including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC Subcommittees may, at times, make recommendations that differ from PTAC's, or from other PTAC Subcommittees', when considering the same evidence.

1.6. PHARMAC considers the recommendations provided by both PTAC and PTAC Subcommittees when assessing applications.

2. Subcommittee Minutes

Cancer Treatment Subcommittee

2.1. The Committee noted the record of the Cancer Treatments Subcommittee of PTAC (CaTSoP) meeting held on 18 October 2019, which included recommendations regarding the following funding applications:

- carfilzomib for relapsed or refractory multiple myeloma,

- daratumumab for relapsed or refractory multiple myeloma,
- pembrolizumab for the adjuvant treatment of resected stage III melanoma,
- rituximab biosimilar,
- trastuzumab biosimilar,
- obinutuzumab for indolent non-Hodgkin lymphoma,
- ribociclib and CDK4/6 inhibitors for HR-positive HER2 negative locally advanced breast cancer, and
- pembrolizumab as a bridge to transplant for relapsed and refractory Hodgkin's lymphoma.

2.2. In regards to item 1 of the CaTSoP meeting record, the role of PTAC Subcommittees and records of meetings, the Committee reiterated the need for clear role delineations between PTAC and Subcommittees, noting the value of their complementary roles, expertise, experience, and perspectives.

2.3. In regards to item 4 and consideration of carfilzomib weekly dosing:

2.3.1. The Committee noted that in February 2019, PTAC had considered carfilzomib for the treatment of relapsed or refractory multiple myeloma and had recommended it be funded with a low priority, subject to Special Authority criteria.

2.3.2. The Committee noted that, in October 2019, CaTSoP had recommended that carfilzomib for the treatment of relapsed or refractory multiple myeloma be listed with a medium priority, subject to Special Authority criteria.

2.3.3. The Committee agreed with the Subcommittee's medium priority recommendation for funding of carfilzomib in this setting, acknowledging CaTSoP's discussion of the ARROW clinical trial and its contextualisation within the therapy area and the New Zealand setting.

2.4. In regards to item 4 and consideration of daratumumab updated information:

2.4.1. The Committee noted that in February 2019, PTAC had considered daratumumab for the treatment of relapsed or refractory multiple myeloma, and recommended the application be deferred pending overall survival data.

2.4.2. The Committee noted that, in October 2019, CaTSoP had considered additional data which included overall survival with 47 months of follow up, as part of an update to the CASTOR study of daratumumab with bortezomib and dexamethasone for the treatment of relapsed or refractory multiple myeloma.

2.4.3. The Committee noted that in October 2019, CaTSoP had recommended that daratumumab for the treatment of relapsed or refractory multiple myeloma be listed with a low priority, subject to Special Authority criteria. The Committee noted that in making this recommendation CaTSoP had considered that although there is evidence of a substantial improvement in progression-free survival (PFS) from daratumumab use in relapsed or refractory multiple myeloma, based on current information, daratumumab would have a very significant impact on the pharmaceutical budget and DHB infusion services; and that both of these were factors in its low priority recommendation.

2.4.4. The Committee noted that the additional information provided by the supplier was not yet in the public domain.

2.4.5. The Committee agreed with CaTSoP that although there was limited overall survival data it did indicate a likely overall survival advantage from the use of daratumumab. However, the Committee considered that there remained uncertainty regarding the magnitude of any effect.

2.4.6. The Committee considered that while further data would be useful to further inform assessment of the efficacy of daratumumab, it agreed with CaTSoP's low priority recommendation and its assessment of the potential impact of daratumumab in terms of the pharmaceutical budget and for DHB infusion services.

2.5. In regards to item 8, obinutuzumab for relapsed/refractory Non-Hodgkin lymphoma and treatment naïve follicular lymphoma:

2.5.1. The Committee noted that in August 2018 PTAC had considered the application for indolent NHL and recommended funding with a low priority, and noted the reasons PTAC had given for its recommendation including that PTAC considered evidence of improved PFS, uncertain evidence of an OS benefit, and no significant difference in safety or HRQoL.

2.5.2. The Committee noted that in August 2018 PTAC had also requested advice from CaTSoP regarding the need for another agent in NHL and the potential impact of increasing infusion requirements due to maintenance therapy.

2.5.3. The Committee noted that in October 2019 CaTSoP had recommended that obinutuzumab in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with indolent non-Hodgkin lymphoma (NHL) who relapsed after, or are refractory to, a rituximab-containing regimen, be funded with a medium priority.

2.5.4. The Committee observed that CaTSoP had not considered any new evidence to that considered by PTAC in August 2018. However, the Committee noted and acknowledged CaTSoP's advice, particularly that detailed in paragraph 8.22 and 8.23, regarding the administration requirements of obinutuzumab, the need of another agent for NHL, and the relevance of the clinical trial evidence from the GADOLIN trial to New Zealand patients.

2.6. In regards to item 9, CDK4/6 inhibitors for the treatment of hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer, the Committee noted that in paragraph 12.43 these agents were described as providing 'around a 30% improvement in OS', but felt more detail would have been useful for PTAC to be able to advise PHARMAC staff about the implications of the magnitude of a survival advantage for decision-making purposes.

2.6.1. Members considered that as written the record with the general statement of a 30% improvement could have been better put in relation to baseline risks, absolute treatment effects such as quantiles of survival, and in relation to uncertainty, such as provided by point estimates and confidence intervals. The Committee noted the corresponding reporting of PFS for the same study in that same paragraph of the record reported an absolute not relative treatment effect (of around 10 or 12 months), and this would have been more useful with further clarification.

2.6.2. The Committee noted that a senior statistician had recently been appointed to CaTSoP; and considered this provided valuable opportunities to discuss and review the most accurate, valid and consistent ways to represent trial results presented in the subcommittee records.

2.6.3. The Committee noted that the overall survival data from MONALESSA-7 did not appear to be referenced in the October 2019 record and so it was unclear whether CaTSoP had reviewed this.

2.6.4. The Committee considered that paragraph 9.33 of the October record should have stated that 'all three MONALEESA studies have shown improved PFS and two an OS benefit'.

2.6.5. The Committee noted that the economic modelling undertaken by PHARMAC for the benefit of CDK4/6 inhibitors for HR-positive HER2-negative locally advanced or metastatic breast cancer used the Kaplan-Meier survival curves in published evidence at source; and considered this to be a sufficiently robust process.

2.7. The Committee noted and agreed with the Subcommittee's recorded considerations and recommendations regarding the remaining items of the October 2019 meeting.

2.8. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, due to their different, albeit complementary, roles, expertise, experience, and perspectives; and that PHARMAC would take into consideration both committees' points of view in its assessment.

Rare Disorders Subcommittee

2.9. PTAC noted the record of the Rare Disorders Subcommittee meeting held on 24 September 2019, where three new funding applications and two resubmissions were considered, and the meeting record included recommendations regarding:

- mercaptamine (cysteamine) hydrochloride 0.55% viscous eye drops for cystinosis,
- nusinersen for the treatment of pre-symptomatic individuals with spinal muscular atrophy and two or three SMN2 copies,
- nusinersen for the treatment of symptomatic patients with type I, II, and IIIa spinal muscular atrophy,
- coenzyme Q10 (CoQ10) for the treatment of CoQ10 deficiency mitochondrial disorders,
- levocarnitine for carnitine deficiency secondary to therapeutic ketogenic diet for intractable epilepsy,
- levocarnitine for inborn errors of metabolism, and
- migalastat and enzyme replacement therapy for Fabry disease.

2.10. The Committee noted the new funding application submitted by a supplier and considered by the Rare Disorders Subcommittee, and agreed with the Rare Disorders Subcommittee recommendation that the application for mercaptamine (cysteamine) hydrochloride 0.55% viscous eye drops (Cystadrops) for cystinosis be declined, based on low quality evidence of benefit and the high proposed cost of Cystadrops compared with the current standard of care (extemporaneously compounded aqueous cysteamine hydrochloride 0.55% eye drops).

2.11. The Committee noted that the Rare Disorders Subcommittee had considered a resubmission from the supplier of nusinersen in relation to two spinal muscular atrophy (SMA) indications. The Committee noted the Subcommittee recommendation that nusinersen be funded with a high priority, within the context of the rare disorders therapeutic area, for the treatment of pre-symptomatic individuals with SMA and two or three SMN2 copies, subject to Special Authority criteria. PTAC noted the Subcommittee's recommendation was based on the absence of funded alternatives, the high health need of these individuals and their family/whānau, longer-term evidence of survival gain and meaningful clinical benefit with nusinersen, and that patients with pre-symptomatic SMA had the greatest potential to benefit.

2.12. The Committee also noted the Subcommittee recommendation that nusinersen be funded with a medium priority, within the context of the rare disorders therapeutic area, for the treatment of symptomatic patients with type I, II, and IIIa SMA, subject to Special Authority criteria. PTAC noted the Subcommittee's recommendation was based on the absence of funded alternatives, the high health need of these individuals and their family/whānau, evidence of survival gain for infantile onset SMA, and meaningful clinical benefit for all symptomatic subgroups considered.

2.13. PTAC noted that, at this February 2020 meeting, it would be considering the funding application for nusinersen for SMA as a separate agenda item (see item 12 for the record of the discussion).

2.14. The Committee noted and agreed with the Subcommittee recommendation that the application for Coenzyme Q10 (CoQ10) for the treatment of CoQ10 deficiency mitochondrial disorders be deferred on the basis of the information supplied. This was a new funding application from a clinician and was considered by the Rare Disorders Subcommittee. PTAC noted that the Subcommittee had made this recommendation because, in order to fully consider this application, a clearer definition of the intended patient population that would benefit from CoQ10 treatment is needed, along with evidence supporting the use of CoQ10 in that patient population, if available.

2.15. The Committee noted and agreed with the Subcommittee recommendation that levocarnitine for carnitine deficiency secondary to therapeutic ketogenic diet for intractable epilepsy be deferred, due to insufficient supporting evidence and uncertainty regarding the size and definition of the intended patient population. This was a new funding application submitted by a clinician and was considered by the Rare Disorders Subcommittee. PTAC noted that the Subcommittee had made this recommendation because, in order to fully consider this application, a clearer definition was needed of the appropriate target patient population e.g. carnitine deficiency due to valproate and plasma carnitine less than 26 micromoles per litre; and evidence of effectiveness or use of levocarnitine in that defined patient population. PTAC advised that PHARMAC could seek advice from paediatric neurologists about the potential group size of patients on a therapeutic ketogenic diet for intractable epilepsy.

2.16. The Committee also noted and agreed with the Subcommittee recommendation that levocarnitine for inborn errors of metabolism be funded with a high priority within the context of the rare disorders therapeutic area, subject to Special Authority criteria. This was a new funding application initiated by PHARMAC and considered by the Rare Disorders Subcommittee. PTAC noted that the Subcommittee had made this positive recommendation because of the high health need of patients, especially those with carnitine transport or uptake deficiencies e.g. systemic primary carnitine deficiency; for whom levocarnitine is the only beneficial treatment, and there is evidence of harm if patients are untreated.

2.17. The Committee noted that the Rare Disorders Subcommittee had considered a resubmission from the supplier of migalastat for the treatment of Fabry disease. The Committee noted the Subcommittee recommendation that migalastat be funded with a medium priority, subject to Special Authority criteria, in the context of the rare disorders therapeutic area and any future funding of an enzyme replacement therapy (ERT) for Fabry disease. Given that migalastat is reportedly only effective in patients with an amenable mutation (approximately 35 - 50% of Fabry patients), PTAC considered that any potential funding considerations for migalastat would be contingent on also considering ERT for Fabry disease; and that it considered this approach would be necessary to ensure equitable access for all Fabry patients. PTAC noted the Subcommittee at its November 2018 meeting recommended funding of ERT for Fabry disease with a medium priority, however, in February 2019 PTAC recommended the application for agalsidase alfa, an ERT for Fabry disease, be declined based on insufficient evidence of long-term beneficial effects on morbidity and mortality. PTAC noted further clinical advice regarding treatments for Fabry disease was not requested from PTAC at this time (February 2020).

2.18. PTAC noted that, in January 2020, PHARMAC had consulted on a proposal to fund ivacaftor for the treatment of cystic fibrosis with the G551D mutation (or other class III gating mutations). The decision for this proposal was subsequently notified on 26 February 2020.

Analgesics Subcommittee

2.19. The Committee noted the record of the Analgesic Subcommittee meeting held on 3 December 2019, which included recommendations regarding:

- lidocaine (lignocaine) gel 2%, urethral syringe for intractable rectal pain/tenesmus,
- doxylamine for the treatment of nausea or vomiting of pregnancy,
- ketamine for intractable pain for patients in the end of life setting,
- clinical advice regarding opioid usage trends,
- a trend of increased use of aprepitant, and
- a trend of increasing use of ondansetron.

2.20. Regarding the application for lidocaine (lignocaine) gel 2 % urethral syringe for intractable rectal pain/tenesmus, the Committee noted the Subcommittee's recommendation (paragraph 4.3), and considered that there is a high unmet health need for people with these symptoms in the end of life setting. The Committee considered that should lidocaine gel be funded for rectal administration there was a high risk of use in people with other indications, for example pruritis ani. The Committee considered that lidocaine gel is associated with a risk of contact dermatitis. The Committee considered it would therefore be appropriate to limit the use of rectal administration of this pharmaceutical to patients in the end of life setting, and that Special Authority criteria would be appropriate in this context.

2.21. Regarding the application for doxylamine for the treatment of nausea or vomiting of pregnancy (paragraph 5), the Committee considered that there is a high health need for severe nausea or vomiting of pregnancy including hyperemesis gravidarum and noted that no treatments, including doxylamine, are currently approved for this indication. However, the Committee was supportive of the Subcommittee's recommendation

2.22. Regarding the Subcommittee's recommendation to fund ketamine via a Special Authority for the treatment of intractable pain in the end of life setting (paragraph 6.11), the Committee noted that it had considered an application for burst therapy in this context at its August 2011 and November 2012 meetings.

2.22.1. The Committee noted that it had recommended for decline, on the basis of evidence of no difference in pain compared to standard care (Hardy et al. J Clin Oncol. 2012 Oct 10;30(29):3611-7), and a higher risk of adverse events. The Committee noted that the Analgesic Subcommittee's recommendation pertained to continuous infusion therapy rather than burst therapy.

2.22.2. The Committee considered that there is an unmet need for patients with intractable pain in the end of life setting, in particular for patients with neuropathic pain who live in locations where they are unable to access a regional anaesthesia service in the community setting.

2.22.3. The Committee considered that in this context, continuous infusion in the end of life setting, ketamine could be used to reduce opioid requirements.

2.22.4. The Committee noted that the Analgesic Subcommittee had not defined specific Special Authority criteria.

2.22.5. The Committee was supportive of the Subcommittee's recommendation and considered that further advice could be sought from the Faculty of Pain Medicine (FPM) of the Australian and New Zealand College of Anaesthetists (ANZCA) and from palliative care clinicians regarding appropriate Special Authority criteria, the likely numbers of patients and duration of treatment. The Committee **recommended** that proposed Special Authority criteria be defined by the Analgesic Subcommittee, and reviewed by PTAC.

2.23. The Committee noted and agreed with the remainder of the record of the 3 December 2019 Analgesic Subcommittee meeting.

2.24. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience; and that PHARMAC would take into consideration both committees' points of view in its assessment.

Immunisation Subcommittee

2.25. The Committee noted the record of the Immunisation Subcommittee of PTAC meeting held on 15 October 2019, which included recommendations regarding:

- influenza vaccination by pharmacists of people with serious mental health conditions or addiction,
- pneumococcal polysaccharide vaccine (PPV23) for patients with untreated chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), and
- the addition of a 15 month pertussis dose to the childhood immunisation schedule..

2.26. The Committee noted and agreed with the Subcommittee's recorded considerations and recommendations regarding the items of the October 2019 meeting.

3. Apalutamide for the treatment of high-risk, non-metastatic, castration-resistant prostate cancer

Application

3.1. The Committee reviewed the application from Janssen for apalutamide for the treatment of high-risk, non-metastatic, castration-resistant prostate cancer (high risk nmCRPC).

3.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

3.3. The Committee **recommended** that the application for apalutamide for high-risk, non-metastatic, castration-resistant prostate cancer (nmCRPC) be deferred, due to the lack of a statistically significant change in overall survival (OS), which the Committee considered to be the primary potential benefit of apalutamide, and no reported evidence for quality of life improvement with apalutamide.

3.4. The Committee requested advice from the Cancer Treatments Subcommittee of PTAC (CaTSoP) regarding: the appropriate timing for its review of this application; likely patient numbers; the impact apalutamide may have on subsequent abiraterone use for patients with metastatic disease; the health need for another agent for high risk nmCRPC in a New Zealand setting; any evidence to support optimal sequencing of this class of agents and abiraterone; the value of metastasis-free survival (MFS) as a surrogate for OS in high risk nmCRPC with supporting evidence for this, views on the proposed Special Authority criteria; and whether there is a class effect from use of these agents.

Discussion

3.5. The Committee noted that in 2017, there were 3,834 new diagnoses of prostate cancer in New Zealand, with the highest number of new cases occurring in men aged 65 to 69 years. The Committee noted that while Māori have a lower incidence rate from prostate cancer than non-Māori men, Māori have a higher mortality rate from prostate cancer than non-Māori (Dachs et al. Lancet Oncol. 2008;9:473-84) and thus higher case-fatality rates,

and Māori are more likely to present with or have detected their prostate cancer later than non-Māori and have more advanced disease at diagnosis (Lao et al. Eur J Cancer Care (Engl). 2016;25:262-8). Members considered that Pacific men have similar incidence of prostate cancer as non-Māori in New Zealand, but typically have worse outcomes from the disease.

3.6. The Committee noted that most patients with non-metastatic prostate cancer receive local treatment (radiation therapy or surgery) and androgen deprivation therapy (ADT) consisting of a gonadotrophin-releasing hormone (GRH) agonist (goserelin, typically injected in the thigh three-monthly), with or without an anti-androgen such as bicalutamide (taken orally daily) commenced at the same time; overall, the aim of this treatment approach is to reduce testosterone to castrate-levels. The Committee noted that castration-resistant prostate cancer (CRPC) is prostate cancer that has become resistant to ADT, signalled by rising prostate-specific antigen (PSA) measurements.

3.7. The Committee noted that the supplier's application defined patients with non-metastatic CRPC (nmCRPC) who are at high risk of developing metastases as those with local (N0) disease or with lymph node involvement (up to N1 staging) and a PSA doubling time (PSADT) of ten months or less. However, the Committee considered that a PSADT of six months or less is more commonly considered to indicate high risk. The Committee considered that Māori may be overrepresented in the group of patients with high risk nmCRPC, although the reasons for this are uncertain and may represent more aggressive disease or that Māori have 'undiagnosed' advanced disease at presentation for care.

3.8. The Committee considered that standard of care management of patients on ADT consists of three- or six-monthly visits with specialist urology and/or specialist radiation oncology and of supportive care provided by primary care physicians for ongoing prescribing of ADT, administration of goserelin and adverse event management. The Committee noted that bicalutamide may be discontinued at patient or clinician discretion, with ongoing goserelin and surveillance for the development of metastatic disease, at which point a patient would be referred to medical oncology to consider treatment with abiraterone (which is currently funded for patients with metastatic CRPC).

3.9. The Committee noted that patients with nmCRPC are generally asymptomatic with good quality of life (QoL) for their age despite expected side effects from ADT or complications from surgical or radiation treatment e.g. incontinence, bowel symptoms or erectile dysfunction. The Committee considered that prevention of metastases is likely to confer a QoL benefit, noting evidence of health utility values in symptomatic patients (0.625) and in asymptomatic or minimally symptomatic patients (0.830) with metastatic CRPC (Lloyd et al. Value Health. 2015;18:1152-7). However, the Committee also noted other evidence of the QoL reduction seen in metastatic disease that suggests overall QoL reduction in men with prostate cancer may be primarily driven by the effects of ADT (Downing et al. Lancet Oncol. 2019;20:436-447).

3.10. The Committee noted that apalutamide is an androgen-receptor inhibitor that binds to the androgen receptor, is then transported into the cell nucleus and affects transcription.

3.11. The Committee noted that apalutamide as a 60 mg tablet presentation is Medsafe-registered for the treatment of patients with nmCRPC.

3.12. The Committee noted that the primary evidence for the health benefits of apalutamide for the treatment of high risk nmCRPC derives from the SPARTAN trial, a randomised (2:1), multicentre, double-blind, placebo controlled, phase III clinical trial of oral apalutamide (240 mg per day) or matched placebo, each in combination with ADT (GnRH agonist with or without an anti-androgen) in 1207 adults with castration-resistant adenocarcinoma of the prostate (Smith et al. N Engl J Med. 2018:378;1408-18). The Committee noted that the treatment was continued until development of metastases, death, discontinuation due to adverse event or consent withdrawal, and median follow-up at analysis was 20.3 months.

3.13. The Committee noted that SPARTAN included participants of median age 74 years, that ~77% of participants had prior local treatment (prostatectomy or radiation therapy) and that ~73% had received a first-generation anti-androgen agent. The Committee noted that patients were defined as being at high risk of developing metastases if they had PSADT ≤ 10 months, that the median baseline PSADT was about 4.5 months, and that participants were stratified by PSADT: (>6 months (29%) vs ≤6 months (71%).

3.14. The Committee noted that metastasis-free survival (MFS, defined as development of metastatic disease or death) was the primary outcome of SPARTAN; the authors' rationale for this being the long OS expected in this population and the supposedly close correlation between MFS and OS in this setting.

3.15. The Committee noted the authors reported the primary outcome after 378 events (184 [22.8%] apalutamide vs 194 [48.4%] placebo) being a median MFS of 40.5 months with apalutamide vs 16.2 months with placebo (hazard ratio [HR] 0.28; 95% CI: 0.23 to 0.35; P<0.001). The Committee noted the incidence of bone metastasis was similar between apalutamide (60.5%) and placebo (54.4%).

3.16. The Committee noted that the median progression-free survival (PFS) at this analysis was 40.5 months with apalutamide vs 14.7 months with placebo; HR 0.29 (95% CI 0.24-0.36), P<0.001.

3.17. The Committee noted SPARTAN also reported PFS2, defined as the time from randomisation to disease progression after a subsequent therapy, which was one of four exploratory only endpoints in the trial. The Committee considered that the PFS2 effects with apalutamide was mostly derived from the PFS effects. The Committee considered the PFS2 results were consistent, with no detrimental impacts with apalutamide on the effects of subsequent treatments.

3.18. The Committee noted that dose reductions occurred in SPARTAN to manage side effects, of which the most common were fatigue, hypertension and rash. The Committee noted that treatment was discontinued due to adverse events (AEs) in 10.6% of apalutamide patients vs 7.0% of placebo patients and that grade 3 or 4 AEs and serious AEs were reported in 45.1% and 24.8% of apalutamide patients and 34.2% and 23.1% of placebo patients, respectively.

3.19. The Committee noted that the mean dose intensity was 218 mg, as calculated by the Therapeutic Goods Administration (TGA) of Australia in their Public Assessment Report for Apalutamide, March 2019 [Internet].

3.20. The Committee noted the results of a prespecified exploratory analysis of health-related quality of life (QoL) in the SPARTAN trial treatment and post-progression follow-up periods (Saad et al. Lancet Oncol. 2018:19;1404-16), and considered that the reporting of QoL as percentages instead of utility values limited the interpretation of this data. The Committee noted that the QoL of patients in SPARTAN was not diminished by treatment with apalutamide compared with placebo, and that the QoL of symptomatic metastatic patients compared with those without metastases was not assessed. The Committee noted that there was no evidence of a QoL benefit from apalutamide in patients with high-risk nmCRPC for whom development of metastasis was delayed, but considered a benefit is possible due to the modest benefit in QoL from MFS in its own right (despite any effects of ADT).

3.21. The Committee noted the results of a second pre-specified interim analysis (IA2) of OS in the SPARTAN trial after median follow-up of 41 months (Small et al. Ann Oncol. 2019:30;1813-20), which were also presented at the 2019 European Society for Medical Oncology (ESMO) annual meeting in Barcelona, Spain. The Committee noted that IA2 had occurred when 285 OS events had accrued; i.e. 65% of the 427 events planned to be used for the planned final OS analysis. The Committee also noted that the four year OS rates were 72.1% with apalutamide compared with 64.7% with placebo, and the hazard

ratio for death with apalutamide compared with placebo was 0.75 (95% CI: 0.59 to 0.96, *P*=0.02), however, this result did not cross the prespecified O'Brien-Fleming boundary of 0.012 and therefore did not meet statistical significance. The Committee noted that no new safety signals were observed at this analysis.

3.22. The Committee noted the SPARTAN trial follow-up data in late years was based on small patient numbers, and considered that the OS data was confounded by subsequent use of other therapies for metastatic CRPC (reported in 40% of apalutamide patients and in 69% of placebo patients; subsequent therapy included abiraterone in ~75% of cases).

3.23. The Committee noted the results of a large, independent study that included meta-analysis of MFS using data from 19 trials that enrolled 12,712 participants with localised prostate cancer from 1987 to 2011, with median follow-up of ten years (Xie et al. J Clin Oncol. 2017;35:3097-104). The Committee noted the correlation between MFS at five years and OS at eight years, and considered that there appeared to be a delayed benefit in terms of OS. The Committee noted that Xie et al. reported that longer MFS correlated with longer OS at least 90% of the time.

3.24. The Committee noted the results of an analysis of MFS and OS from the SPARTAN trial, which reported reduced life expectancy following development of metastasis and suggested a close relationship between MFS and OS in high risk nmCRPC (Smith et al. Clin Genitourin Cancer. 2019; pii: S1558-7673(19)30334-9. [Epub ahead of print]). The Committee noted that the analysis was performed using a different method to that of Xie et al. and that the authors reported MFS-OS correlation values that unexpectedly differed between treated patients (0.89) and untreated patients (0.35).

3.25. The Committee noted that, although there is currently no evidence from head to head comparisons, the available data for MFS suggests there is a class effect for this generation of non-steroidal anti-androgen agents i.e. apalutamide, darolutamide (ARAMIS trial; Fizazi et al. N Engl J Med. 2019;380:1235-46) and enzalutamide (PROSPER trial; Hussain et al. N Engl J Med. 2018;378:2465-74), which each reported increases in median MFS of between 21.9 to 24.3 months compared with placebo. Members noted that there is evidence from indirect comparisons between apalutamide and enzalutamide, of which two have reported no difference in MFS (Riaz et al. J Clin Oncol. 2019;7 suppl.263; Wallis et al. Eur Urol Oncol. 2018;1:238-41) and a third, sponsored by Janssen, was a matching-adjusted comparison that still failed to show significant differences in MFS and OS but which, nevertheless, concluded that OS was more likely to be superior with apalutamide treatment when compared with enzalutamide treatment; the Committee considered this conclusion was not credible (Chowdhury et al. Adv Ther. 2020;37:501-11).

3.26. The Committee considered that the strength of the relationship between MFS and OS in nmCRPC is not yet clearly defined, and that any correlation is complicated by the likely delayed benefit and by the confounding use of subsequent therapies. Members also considered that challenges associated with use of MFS as a surrogate for quality-adjusted life years (QALYs) limit the utility of MFS as an interim outcome measure.

3.27. The Committee noted that enzalutamide has not yet demonstrated an OS benefit in the PROSPER trial (after approximately 41 months of follow-up) despite showing MFS benefit, although this may be due to a delayed effect.

3.28. Members noted evidence that the acquired F876L androgen receptor mutation in advanced prostate cancer cells confers resistance to enzalutamide and may also convey resistance to apalutamide, but considered that it appears that darolutamide may not be similarly affected by the F876L mutation or other known androgen receptor mutations (Korpal et al. Cancer Discov. 2013;3:1030-43; Fujita et al. World J Mens Health. 2019;37:288-95).

3.29. The Committee considered that the evidence from the SPARTAN trial for MFS was of high strength and quality, however, the evidence for OS benefit was of uncertain strength and low quality. This was due to the lack of a statistically significant difference in OS, which could relate to the control needed for multiple sequential analyses from having pre-specified interim analyses (Type I error inflation), insufficient OS events accruing for final analysis, and the confounding impact of subsequent therapies; and that the study was not powered to meet the specific endpoint of OS (OS being simply a secondary endpoint, alongside four others).

3.30. The Committee considered that based on the currently available trial data (noting the TITAN trial evidence in metastatic CRPC, which reported a statistically significant OS benefit with apalutamide at two years), it appears that apalutamide may confer a delayed OS benefit in high risk nmCRPC; but that, as the OS data for apalutamide is currently immature, the final OS analysis of the SPARTAN trial would be required to inform the magnitude of any OS benefit in this setting.

3.31. The Committee reiterated its view (paragraph 8.20 above) that the strength of the relationship between MFS and OS in nmCRPC remained to be clearly defined, and limits to its usefulness of MFS as a surrogate outcome.

3.32. The Committee considered that ADT alone would be the current standard of care comparator for patients with high risk nmCRPC.

3.33. The Committee considered that, if funded, the addition of apalutamide to ADT in high risk nmCRPC would delay but not otherwise change the usage of abiraterone in metastatic CRPC. However, the Committee considered that there was insufficient evidence to confidently inform whether apalutamide would affect the magnitude of benefit seen with subsequent abiraterone treatment.

3.34. The Committee considered that apalutamide use would be unlikely to change the healthcare resource required for active monitoring of patients with high risk nmCRPC to detect development of metastatic disease e.g. laboratory tests and radiological assessments, but considered that additional GP visits may be required to manage adverse events such as hypertension and rash. Members considered that private use of PSMA-PET scans for prostate cancer is increasing, and it is unclear what impact the funding of apalutamide may have on the use of such testing in DHBs.

4. Bedaquiline for the treatment of rifampicin-resistant and multi drug-resistant tuberculosis

Application

4.1. The Committee reviewed the clinician application for bedaquiline in the treatment of multidrug-resistant and rifampicin-resistant tuberculosis (MDR-TB and RR-TB)

4.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

4.3. The Committee **recommended** that bedaquiline be funded with a **high priority** for the treatment of multidrug-resistant tuberculosis (MDR-TB) based on high health need and good evidence supporting the efficacy and safety of bedaquiline.

4.4. The Committee noted that in making the above recommendation, it was important to consider the recent update in MDR-TB treatment guidelines from the World Health Organization, which included bedaquiline as one of the Group A agents in the MDR-TB treatment regimen. The Committee considered that bedaquiline for the treatment of MDR-TB should be listed subject to the following Special Authority criteria:

BEDAQUILINE – Special Authority for Subsidy
Initial application – (tuberculosis - multidrug-resistant). From any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1. The patient has multidrug-resistant tuberculosis (MDR-TB); and
2. The Ministry of Health's Tuberculosis Clinical Network has reviewed the patient case and recommends bedaquiline as part of the treatment regimen.

4.5. The Committee considered that PHARMAC could seek advice from the National Tuberculosis Clinical Network to clarify whether rifampicin-resistant tuberculosis (RR-TB) should be treated with the same regimen and circumstances with bedaquiline as for MDR-TB.

Discussion

4.6. The Committee noted that tuberculosis (TB) is a bacterial infection caused by *Mycobacterium tuberculosis* and is a leading cause of morbidity and mortality worldwide. The Committee considered that TB poses a great public health risk of spread if the index case is not adequately treated, as one person with active TB can infect more than one in four of their close contacts.

4.7. The Committee noted that MDR-TB is defined as resistant to two essential first-line tuberculosis treatments as prescribed by the Ministry of Health (MOH) tuberculosis guidelines (sourced from the World Health Organization [WHO]), isoniazid and rifampicin. The Committee noted MDR-TB has a high mortality rate of 40%, and that 5% of all cases of tuberculosis are classed as MDR-TB but they account for about a third of the total healthcare cost of tuberculosis.

4.8. The Committee noted the treatment regimen from the latest guidelines from the WHO published in 2019 (WHO consolidated guidelines on drug-resistant tuberculosis treatment) comprising of three Group A agents, a fluoroquinolone (either levofloxacin or moxifloxacin), bedaquiline and linezolid, and two Group B agents, clofazimine and cycloserine. The Committee noted that Group C agents should only be used in place of Group A or B agents if they are contraindicated.

4.9. The Committee noted that bedaquiline 100 mg tablet had been approved by Medsafe in 2016. The Committee noted that bedaquiline is indicated in adults (>18 years) as part of a combination therapy of MDR-TB. The Committee also noted the approved dosing regimen of 400 mg (four tablets) once daily for two weeks, then 200 mg (two tablets) three times per week with at least 48 hours between doses.

4.10. The Committee considered the duration of treatment for bedaquiline as a period of 24 weeks. The Committee noted the advice to discontinue bedaquiline four to five months prior to discontinuing other drugs in the treatment regimen, as bedaquiline has a terminal half-life of four to five months which risks antimicrobial resistance to bedaquiline developing if other agents are taken for insufficient time after stopping bedaquiline.

4.11. The Committee noted that a funding application for bedaquiline for the treatment of MDR-TB has been considered by PHARMAC previously. The Committee noted that the Rare Disorders Subcommittee considered the application at its November 2014 meeting and recommended that the Anti-Infective Subcommittee be asked for clinical advice regarding appropriate restrictions on the use of bedaquiline and whether there would be any safety concerns with listing bedaquiline. The Committee noted that the Anti-Infective Subcommittee recommended bedaquiline be funded with a high priority for the treatment of extensively drug-resistant tuberculosis (XDR-TB), on the recommendation of the Ministry of Health MDR-TB Committee at its December 2014 meeting. The Committee noted that both the Anti-Infective Subcommittee and the Rare Disorders Subcommittee noted the unexplained increased mortality in the bedaquiline group in the phase-II, placebo-controlled, double-blind, randomised trial by Diacon et al (N Eng J Med. 2014;371:723-32). The Committee noted that it had previously reviewed and accepted the

minutes from the respective PTAC Subcommittees (PTAC February 2015 minutes, PTAC May 2015 minutes).

4.12. The Committee noted the latest WHO guidelines, which incorporate a meta-analysis of 13,104 patient level data records from 53 studies in 40 countries investigating bedaquiline in MDR-TB. The Committee noted the rate of treatment failure was lower in patients receiving bedaquiline (11.6%) compared with those who did not (48.8%). The Committee noted that treatment failure would require further treatment with other toxic medications and result in patient seclusion/isolation for longer duration of time, especially in regions without infection control isolation facilities with adequate negative pressure etc. The Committee noted that fewer deaths were observed with those taking bedaquiline (15%) when compared with those not taking bedaquiline (22.8%).

4.13. The Committee noted the results from a phase-II, placebo-controlled, double-blind, randomised trial with 208 participants to evaluate the anti-bacterial activity of bedaquiline as part of a combination therapy of MDR-TB (Diacon et al, N Eng J Med. 2014;371:723-32). The Committee noted the reduction in the median time to culture conversion in the bedaquiline group (83 days) compared with the placebo group (125 days). The Committee also noted the higher rates of cure observed in the bedaquiline group (58%) compared with placebo group (32%).

4.14. The Committee noted the results from a phase-II, multicentre, open label, single arm study with 241 participants to evaluate the efficacy of bedaquiline as part of an individualised MDR-TB treatment regimen (Pym et al, Eur Respir J. 2016;47(2):564-74). The Committee noted the proportion of patients in the bedaquiline group with confirmed culture conversion at weeks 24 in C209 (79.5%) was similar to that of C208 (72.2%). The Committee also noted the higher rates of cure observed in the bedaquiline group (61%) compared with the placebo group (57.6%). The Committee noted that none of the deaths observed in the bedaquiline group appeared directly related to bedaquiline; reported causes of death included tuberculosis-related illness, haemoptysis, renal impairment, respiratory failure, congestive cardiac failure, and hypertension.

4.15. The Committee noted the results from a meta-analysis based on pooled data from five cohorts of 537 patients treated with bedaquiline in France, Georgia, Armenia, and South Africa (Lawrence et al, Emerg Infect Dis. 2019 May; 25(5): 936–943). The Committee noted positive results for rate of culture conversion at 6 months (78%), treatment success (65.8%) and death (11.7%). The Committee also noted that the results were positive despite many patients suffering from “cavitating diseases” such as HIV (120 patients) and extensively-drug resistant tuberculosis (77 patients).

4.16. The Committee noted the following evidence for bedaquiline as part of MDR-TB treatment regime:

4.16.1. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort (Guglielmetti et al. Clin Infect Dis. 2015;60(2):188-94).

4.16.2. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study (Schnippel et al. Lancet Respir Med. 2018;6(9):699-706), in which 24,014 tuberculosis cases were registered in the EDRweb between 1 July 2014 and 31 March 2016, with 19,617 patients initiated treatment and meeting analysis eligibility criteria. Bedaquiline-containing regimens were given to 743 (4.0%) patients with MDR-TB or RR-TB. Of the 1016 patients who received bedaquiline, 128 died (12.6%); the Committee noted that 4,612 deaths (24.8%) occurred among 18,601 patients on the standard regimens. Bedaquiline was therefore associated with a two-thirds reduction in the risk of all-cause mortality for patients with multidrug-resistant or rifampicin-resistant tuberculosis (hazard ratio 0.35, 95% CI 0·28–0·46) compared with standard regimens.

4.17. The Committee noted one randomised controlled trial submitted by the applicant, but that several non-randomised studies have supported the evidence for bedaquiline as part of individualised multidrug MDR-TB treatment regimen. The Committee noted that in order to comply with the latest guidelines from the World Health Organization, bedaquiline would need to be made available for the treatment of MDR-TB.

4.18. The Committee considered the use of amikacin, one of the second-line anti-tuberculosis agents, as an alternative to bedaquiline. The Committee considered that although this Group C agent has comparable efficacy to Group A agents, amikacin has an unfavourable toxicity profile, being associated with renal impairment, hearing loss and vestibular dysfunction.

4.19. The Committee considered the cardiovascular toxicity profile of bedaquiline, noting that it prolongs the QT interval, especially in combination with moxifloxacin. The Committee noted that very few people stop bedaquiline due to cardiotoxicity, although patients may switch from moxifloxacin to levofloxacin to reduce the combined effect on QT interval. The Committee noted that all patients on bedaquiline would require ECG and serum electrolyte monitoring in line with established guidelines.

4.20. The Committee considered that bedaquiline results in a more rapid culture conversion compared with other agents, and this in turn would reduce the isolation time required in hospital i.e. being infected with a difficult to treat fatal organism prior to culture conversion. The Committee considered bedaquiline may also lessen the risk of transmission to healthcare workers and other members of the community, where generally patients could be treated in outpatient and community settings. The Committee noted that bedaquiline enables outpatient oral treatment for extrapulmonary TB and pulmonary TB that is no longer infectious.

4.21. The Committee considered there would be positive health outcomes and reductions in total healthcare costs by adding bedaquiline to current treatment regimens. The Committee noted the potential reduction in total healthcare costs and increased disability-adjusted life years when bedaquiline is added to the individualised MDR-TB treatment regimen.

4.22. The Committee considered that resistance to anti-tuberculosis agents is increasing globally, which may impact on the number of imported cases seen in New Zealand. The Committee considered that the expected number of cases in New Zealand could be approximately 4-7 per year.

4.23. The Committee noted that over 78% of TB patients are born outside of New Zealand, and the highest incidence rates of MDR-TB is observed mainly in refugee populations. The Committee considered that MDR-TB does not have a disproportionate impact on Māori health.

5. Esketamine for treatment - resistant depression

Application

5.1. The Committee reviewed the application from Janssen for esketamine for treatment-resistant depression.

5.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

5.3. The Committee **recommended** that the application for esketamine for treatment-resistant depression be declined due to:

5.3.1. the evidence did not demonstrate a clear meaningful clinical benefit in differences between intervention and control groups in primary outcomes (reductions in end scores), combined with the relatively short duration of such trials in relation to the duration of depression;

5.3.2. the low strength of evidence in the New Zealand clinical setting due to the practical difficulties in implementing treatment with esketamine, in particular the health sector's capacity (time and skills) to diagnose treatment-resistant depression accurately; and the risk that this may delay patients with severe depression from accessing effective treatment that has a strong evidence base;

5.3.3. the risk of very high uptake based on a diagnosis of depression with suicidality, preventing access to other potentially more effective and established interventions;

5.3.4. the moderate to high risk to the individual and society regarding potential misuse or diversion despite the supplier's proposed risk management plan;

5.3.5. the absence of exit criteria in the supplier's proposed Special Authority or a clear clinical rationale for stopping treatment with esketamine, which could result in patients remaining on esketamine indefinitely; and

5.3.6. the uncertainty about the potential for long-term dependence and tolerance to esketamine.

5.4. In making this recommendation, the Committee also considered that there was a high risk that patients may inappropriately receive esketamine ahead of other more suitable treatments and strategies e.g. non-pharmacological interventions or augmentation of current therapies, as a result of the relatively low barrier proposed by the supplier for access to esketamine (primarily being failure of two antidepressants) and resource limitations in primary care for managing patients with treatment-resistant depression.

Discussion

5.5. The Committee noted that treatment-resistant depression was defined in the supplier's application as failure of two different pharmacotherapies, which is consistent with the Royal Australian and New Zealand College of Psychiatrists (RANZCP) definition. The Committee noted that ketamine (or its enantiomers) are not currently included in the RANZCP guidelines for treatment-resistant depression. The Committee noted that in clinical practice, often patients have not been tried on adequate doses and durations of antidepressants and in a New Zealand setting this can make it difficult to identify patients whose depression is treatment-resistant.

5.6. The Committee noted that relative to other countries, New Zealand has a high burden of mental health conditions. The Committee noted approximately 16% of New Zealanders experience depression in their lifetime and approximately 30% of patients with depression are reported to be treatment-resistant, equating to approximately 350,000 patients with depression and 110,000 with treatment-resistant depression in New Zealand. Members also noted that treatment-resistant depression is not necessarily severe depression; treatment-resistant depression can present as mild, moderate or severe.

5.7. The Committee noted that patients with depression can experience symptoms such as a persistent sad, anxious or empty mood, feelings of worthlessness, fatigue, difficulty concentrating, and insomnia. The Committee noted that women, Māori, people living in rural areas and people with chronic physical illness and cancer are disproportionately affected by depression. The Committee noted that patients with treatment-resistant depression are not able to achieve relief from these symptoms and therefore the disease impacts this population to a great extent, resulting in a high health need and a high burden of disease. The Committee also noted that there are also significant emotional,

psychiatric, existential and financial health needs for the families and whānau of people with treatment-resistant depression.

5.8. The Committee noted that PHARMAC currently funds 16 antidepressants, that primary health organisations and district health boards (DHBs) fund psychotherapy, and that electroconvulsive therapy (ECT) is available in all DHBs. The Committee considered that there are currently no issues with access to funded pharmacological treatments for treatment-resistant depression or to ECT. The Committee recognised that access to psychological interventions could be a barrier.

5.9. The Committee noted that esketamine is the S-enantiomer of ketamine and is a non-selective, non-competitive, antagonist of the N-methyl-D-aspartate receptor. The Committee noted that esketamine is Medsafe-approved for treatment-resistant depression in adults in conjunction with a newly initiated oral antidepressant. The Committee noted that esketamine is administered by intranasal spray (in single dose devices) and that the supplier advises that this is to be under the supervision of a healthcare professional, with a dosing frequency ranging from twice weekly to fortnightly. The Committee noted that the supplier advises patients need to be observed by a healthcare professional for two hours following every treatment to monitor for adverse events (preferably in a quiet room in a reclining chair) and that patients should not drive for 24 hours following each treatment.

5.10. The Committee considered that the supervised administration and post-treatment observation requirements proposed by the supplier would have significant resource implications for healthcare providers, especially in primary care and community pharmacies, and may also be a barrier for patients. The Committee considered that there was no clear evidence that esketamine would reduce hospital stays for patients with treatment-resistant depression.

5.11. The Committee noted that the key evidence for esketamine comes from four randomised, double-blind, active-control clinical trials: TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, and SUSTAIN-1. Each trial investigated the use of intranasal esketamine with a newly initiated antidepressant, compared with intranasal placebo with a newly initiated antidepressant, in adults with treatment-resistant depression. SUSTAIN-1 was a withdrawal trial and all the TRANSFORM trials were active treatment trials.

5.12. The Committee noted the TRANSFORM-1 trial assessed 346 patients with recurrent treatment-resistant depression, treated with 56 mg esketamine, 84 mg esketamine or placebo, all as twice weekly treatments (Fedgchin et al. Int J Neuropsychopharmacol 2019;22:616-30). The Committee noted that a statistically significant Montgomery-Asberg Depression Rating Scale (MADRS) score difference was not observed between the esketamine 84 mg and control group after 28 days of treatment (-3.2, 95% CI: -6.88, 0.45; p=0.088). The Committee noted that the authors did not formally evaluate the 56 mg group compared with controls, due to lack of statistically significant result of 84 mg group.

5.13. The Committee noted the supplier-sponsored TRANSFORM-2 trial assessed 223 patients with single-episode or recurrent moderate to severe depression with a history of treatment-resistant depression, treated with 56 mg esketamine, 84 mg esketamine or placebo twice weekly (Popova et al. Am J Psychiatry. 2019;176:428-38). The Committee noted TRANSFORM-2 allowed for dose escalation, unlike TRANSFORM-1 where the doses were fixed. The Committee noted both the esketamine and placebo groups were observed to have a reduction in MADRS score, but considered that the main driver of this reduction was unclear; the Committee could not determine if the reduction in MADRS was related to the new antidepressant or esketamine. The Committee noted no subgroup analysis by new drug was undertaken (and considered the trial would not have been powered for this). The Committee noted the statistically significant reduction in MADRS score of four points in the esketamine group compared with placebo after 28 days of treatment (95% CI: -7.31, -0.64; p=0.020) and that this was less than the absolute reduction in MADRS scores in both groups from initiation to end point. The Committee

noted that for the treatment regimes used in Transform-2 (and other TRANSFORM trials) do not reflect the funded New Zealand clinical environment.

5.14. The Committee noted the TRANSFORM-3 trial assessed 138 patients aged ≥65 years with recurrent, moderate to severe treatment-resistant depression treated with 28 mg, 56 mg, or 84 mg esketamine or placebo twice weekly (Ochs-Ross et al. Am J Geriatr Psychiatry. 2019;28:121-41). The Committee noted that a statistically significant difference in MADRS score was not observed (least square mean of -3.6 (95% CI: -7.20, 0.07; p=0.059)) between the esketamine and placebo groups after 28 days of treatment, however, members considered this was likely due to the small sample size.

5.15. The Committee noted that two of the three TRANSFORM trials did not reach statistical significance in their primary end points.

5.16. The Committee noted the SUSTAIN-1 trial assessed 297 patients who had achieved response or remission from esketamine treatment and investigated relapse rates in patients who continued esketamine treatment compared to a change to placebo treatment (Daly et al. JAMA. 2019; 76:893-903). The Committee noted that study participants were only required to have one oral antidepressant fail them, and that this did not align with the population defined in the supplier's application. The Committee noted the failure to accrue the numbers of patients required by the study's power calculations. The Committee also noted stable remitters and responders who continued to receive esketamine relapsed significantly less than patients who were randomised to placebo (stable remission: 26.7% esketamine vs 45.3% placebo relapsed (HR, 0.49, 95% CI, 0.29, 0.84; P=0.003); stable response patients: 25.8% esketamine vs 57.6% placebo (HR, 0.3; 95% CI, 0.16, 0.55; P<0.001). The Committee noted that 82.2% of the esketamine group experienced adverse events compared with 45.5% of the placebo group.

5.17. The Committee considered that the evidence from the above clinical trials was of good quality generally, but this quality translated poorly to the New Zealand setting. The Committee noted poor outcome strength in the trials, and the relatively short duration of such trials relative to the duration of depression. The Committee questioned whether the four trials adequately demonstrated clinically meaningful improvements in patient outcomes, even in those trials that reached statistical significance. The Committee considered that it was difficult to clearly ascertain from the trials what proportion of treatment benefit was due to esketamine and what was due to the new oral antidepressant agent commenced at the same time as esketamine.

5.18. The Committee noted a research article by Leucht et al (J Aff Disord. 2017;210:287-93) that was not included in the supplier's application and the authors included Janssen employees; the article reported that a reduction in MADRS score of eight or greater indicated depression remission. The Committee considered a MADRS reduction of eight or greater was needed to represent a clinically meaningful response, particularly in light of clinical trials that show absolute reductions in excess of 12 in treatment and placebo arms. The Committee noted that the MADRS is not commonly employed in clinical practice and becomes less reliable with repeated use, which would result in considerable practical difficulties in the use of the scale as a monitoring tool in a New Zealand clinical setting, with particular challenges for test-retest and inter-rater reliabilities.

5.19. The Committee considered it is well recognised that when patients are enrolled in a clinical trial for depression, an improvement in their depressive symptoms is often observed. A similar positive effect is seen in clinical practice for patients with depression who have regular contact with healthcare services. Members considered that this effect could also occur with esketamine in clinical practice, due to the once or twice weekly dosing and post-administration supervision recommended by the supplier.

5.20. The Committee noted adverse events such as dissociation, somnolence and dizziness observed with esketamine treatment were demonstrated in all clinical trials. The Committee considered that trial participants were unlikely to have been adequately

blinded due to the adverse events associated with esketamine treatment. The Committee also considered that maintaining blinding in any esketamine trial on this basis would be very difficult.

5.21. The Committee noted that ketamine is used recreationally for its dissociative effects, and considered that these effects of esketamine may encourage its long-term use. The Committee noted the long-term implications of esketamine use are unclear, with long-term safety data not yet available. Members considered that patients may develop tolerance to esketamine over time and that this would result in higher doses needing to be prescribed, over and above the maximum 84 mg (three devices) twice weekly dose proposed by the supplier.

5.22. The Committee noted that ketamine is a drug of abuse and that esketamine has the same potential to be abused. The Committee considered that esketamine may in fact have a higher abuse potential than ketamine. Both of these drugs are classified as a Class 4 Controlled Drugs. The Committee noted the supplier had proposed a risk mitigation plan (RMP) to reduce the risk of misuse of esketamine. The RMP proposed to exclude patients with a history of drug or alcohol misuse from being prescribed esketamine, that dispensing and administration of esketamine would occur only by appropriately trained healthcare professionals at approved health centres, that there would be a restricted supply chain with surveillance and stock distribution to RMP-trained sites only, and the device is designed to minimise residual misuse.

5.23. The Committee considered that, contrary to the supplier's proposed RMP, in practice some patients would likely be dispensed esketamine to take home, which would increase the risk of misuse and/or diversion. The Committee considered that excluding patients with alcohol and drug history from being prescribed esketamine would likely make little difference to the potential for misuse and could be discriminatory to a high-need vulnerable population that has high mental health co-morbidities. The Committee noted that, despite the RMP, there is no technical requirement to adhere to this plan, and considered that the implementation of such a RMP in New Zealand would be impractical and would likely carry a significant cost.

5.24. The Committee considered that the supplier may have underestimated the infrastructure services needed to support the safe use of esketamine. The Committee considered that esketamine would have a significant impact on health sector expenditure and result in a high resource burden due to the risk of misuse, device disposal costs, approved facilities for the supervision of administration and post-treatment monitoring, managing pharmacy requirements for controlled drugs, and increased demand for mental health specialist services.

5.25. The Committee noted that there were significant costs related to the post-administration monitoring period recommended by the supplier, including two hours of supervision and blood pressure monitoring by a health professional, and restrictions on patients as they are unable to drive for 24 hours after each treatment session (the latter could be especially problematic for patients who live rurally). The Committee also noted that the post-administration effects of esketamine may also impair the ability of patients to undertake other activities, such as being a care-giver for family members including children. The Committee also noted the environmental impact of single-use devices, particularly given that some patients would require three devices up to twice weekly.

5.26. The Committee noted that best clinical practice approaches to the management of patients with treatment-resistant depression involve reassessing the diagnosis, then optimising the dose and duration of antidepressant, and considering what adjunctive treatment would be appropriate including psychosocial support. Members noted that this comprehensive management approach would require doctor appointments considerably longer than the standard 15 minutes usually provided by general practitioners. The Committee noted that this is generally a specialist assessment and requires more time.

The Committee noted that there has been a significant increase in people referred to secondary care mental health services.

5.27. The Committee considered that due to the resource demands on primary and secondary healthcare services, there is a risk that patients may be commenced on esketamine by their general practitioner ahead of a thorough reassessment of diagnosis or other clinical approaches being implemented to manage depression, and this would have the effect of increasing the risk of inappropriate prescribing and increasing the size of the patient population that could be prescribed esketamine. The Committee considered that up to 80% of patients with depression would describe suicide ideation at some point and this would make them eligible for esketamine, significantly increasing the eligible patient pool.

5.28. The Committee considered that current standard of care management of patients with treatment-resistant depression would consist of assessment by a secondary care professional with dose adjustment and modification of a patient's pharmacotherapy, and that this management would be the appropriate comparator in the requested patient population.

5.29. The Committee considered that prescribing esketamine in a primary care setting may present significant risks to best clinical management of patients, noting that there are varying severities of treatment-resistant depression. The Committee noted that the supplier proposes esketamine treatment be initiated either by a psychiatrist or by a medical practitioner who has consulted with a psychiatrist. Members considered that it would be clinically difficult for psychiatrists to make and/or confirm a diagnosis of treatment-resistant depression via a telephone conversation with the patient's general practitioner; and that a diagnosis of treatment-resistant depression by a psychiatrist can only be made adequately by assessing the patient directly. The Committee considered that this pressure on primary care resource and limited consultation with a psychiatrist may lead to inappropriate use of esketamine when alternative treatment options e.g. non-pharmacological interventions or augmentation of current therapies, may be more clinically suitable.

5.30. The Committee noted the supplier had proposed Special Authority criteria, however, members considered these had a number of practical limitations, including the requirement that esketamine be initiated by a psychiatrist or on the advice on a psychiatrist. As noted above, the adequate diagnosis of treatment-resistant depression in a New Zealand setting requires assessment by a psychiatrist, and there are health sector resource constraints on accessing a psychiatrist. The Committee noted the proposed Special Authority criteria excluded patients who are current or previous users of illegal drugs, and as noted above this patient group often has high health needs. Under the proposed criteria, the supplier indicated about 10,000 patients could be eligible for treatment with esketamine, however, the Committee considered that potentially all patients with treatment-resistant depression (110,000) could be eligible and access esketamine, and this number could increase significantly if patients with a single episode of depression with suicidality were added. The Committee noted that there were no exit or stopping criteria proposed by the supplier, and that this could potentially result in patients remaining on esketamine indefinitely.

5.31. The Committee noted that mental health is currently a Government priority, however members considered that funding another pharmacotherapy, such as esketamine, may not be the best mechanism to achieve a clinically meaningful, positive impact for New Zealanders with treatment-resistant depression. The Committee considered that esketamine would not offer significant health benefits over the funded pharmacotherapies, due to the lack of meaningful clinical benefit in the New Zealand setting and the associated risks of esketamine use to individuals and society.

5.32. Members noted that treatment-resistant pain has contributed to significant opioid dependency in society, and considered that there may be a risk of a similar impact occurring with esketamine for treatment-resistant depression.

5.33. The Committee also considered that esketamine would not meet any unmet health need in treatment-resistant depression, and that any new investment would be more beneficially directed to supporting and strengthening mental health services in the community where there is a clearly recognised and significant unmet health need and to increasing access to secondary care services where, due to health sector resource constraints, it is difficult to access a psychiatrist.

6. Nusinersen for the treatment of Spinal Muscular Atrophy

Application

6.1. The Committee reviewed the application for nusinersen in the treatment of spinal muscular atrophy

6.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

6.3. The Committee **recommended** that nusinersen be funded with a high priority for the treatment of pre-symptomatic individuals with spinal muscular atrophy who have only two or three SMN2 copies, subject to the Special Authority criteria below. This recommendation was based on the absence of funded alternatives, the high health need of these individuals and their family/whanau, and magnitude of potential health benefit.

6.4.

Initiation – spinal muscular atrophy (SMA) – pre-symptomatic

Applications only from, or in consultation with, a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.

Re-assessment required after 12 months

All of the following:

1. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygous mutation, identified via newborn screening; and
2. Patient must be pre-symptomatic; and
3. Patient must have only two or three copies of *SMN2*; and
4. Treatment must be given concomitantly with standard of care for this condition; and
5. Treatment must not exceed four loading doses (at days 0, 14, 28 and 63); and
6. Patient must be 18 years of age or under.

Continuation – spinal muscular atrophy (SMA) – pre-symptomatic

Applications only from, or in consultation with, a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.

Re-assessment required after 12 months

All of the following:

1. Patient must have had a previous approval for nusinersen; and
2. Treatment must be given concomitantly with standard of care for this condition; and
3. There has been demonstrated maintenance of motor milestone function (as assessed using age-appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation; and
4. The patient does not require non-invasive permanent assisted ventilation (see Note).

Note:

Non-invasive permanent assisted ventilation means: Breathing support administered via nasal cannula or face mask for greater than or equal to 16 hours per day

6.5. The Committee **recommended** that nusinersen be funded with a high priority for the treatment of symptomatic individuals with spinal muscular atrophy type I, II or IIIa prior to 3 years of age, subject to the Special Authority criteria below. This recommendation was based on the absence of funded alternatives, the high health need of these individuals and their family/whanau; and, that although the magnitude of potential health benefit was unlikely to be as large, when compared with the pre-symptomatic population, this group represented the current prevalent population being cared for by the health sector.

Initiation – spinal muscular atrophy (SMA) – symptomatic type I, II and IIIa

Applications only from or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.

Re-assessment required after 12 months
All of the following:

1. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygous mutation; and
2. Patient must have experienced the defined signs and symptoms of SMA type I, II or IIIa prior to 3 years of age (see Notes); and
3. Treatment must be given concomitantly with standard of care for this condition; and
4. Treatment must not exceed four loading doses (at days 0, 14, 28 and 63); and
5. Patient must be 18 years of age or under.

Continuation – spinal muscular atrophy (SMA) – symptomatic type I, II and IIIa
Applications only from, or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.
Re-assessment required after 12 months

All of the following:

1. Patient must have had a previous approval for nusinersen; and
2. Treatment must be given concomitantly with standard of care for this condition; and
3. There has been demonstrated maintenance of motor milestone function (as assessed using age-appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation; and
4. Treatment must be ceased when non-invasive permanent assisted ventilation (see Note) is required in the absence of a potentially reversible cause while being treated with this drug.

Notes:
Non-invasive permanent assisted ventilation means:
Breathing support administered via nasal cannula or face mask for greater than or equal to 16 hours per day.

Defined signs and symptoms of type I SMA are:
i) Onset before 6 months of age; and
ii) Failure to meet or regression in ability to perform age-appropriate motor milestones.

Defined signs and symptoms of type II SMA are:
i) Onset between 6 and 18 months; and
ii) Failure to meet or regression in ability to perform age-appropriate motor milestones.

Defined signs and symptoms of type IIIa SMA are:
i) Onset between 18 months and 3 years of age; and
ii) Failure to meet or regression in ability to perform age-appropriate motor milestones

Discussion

6.6. The Committee noted that the Rare Disorders Subcommittee had first reviewed a funding application for nusinersen for symptomatic type I, II and IIIa spinal muscular atrophy (SMA) in November 2018 and that at this time the Subcommittee recommended that the application be deferred until longer-term data were published from the SHINE and/or NURTURE trials.

6.7. The Committee noted that it subsequently reviewed the Record of the November 2018 Rare Disorders Subcommittee in February 2019, and agreed with the Subcommittee's recommendation to defer a decision on nusinersen until longer-term follow up analyses

were available. The Committee noted that it had also recommended that consideration of interim analyses of the key trials should be delegated to the Rare Disorders Subcommittee and the Subcommittee could then consider if this data was sufficiently mature to be brought back to the Committee.

6.8. The Committee noted that a resubmission from the Supplier, which included longer-term data from the SHINE and NURTURE trials, was considered by the Rare Disorders Subcommittee at its September 2019 meeting. The Committee noted that based on the updated evidence provided in the resubmission the Subcommittee had recommended the following:

6.8.1. That nusinersen be funded with a high priority, within the context of the rare disorders therapeutic area, for the treatment of pre-symptomatic individuals with SMA and two or three SMN2 copies, subject to Special Authority criteria; and

6.8.2. That nusinersen be funded with a medium priority, within the context of the rare disorders therapeutic area, for the treatment of symptomatic patients with type I, II and IIIa SMA, subject to Special Authority criteria

6.9. The Committee noted that the Subcommittee's different funding priorities (high for pre-symptomatic and medium for symptomatic) were largely based on pre-symptomatic patients having longer-term evidence of survival gain and having the greatest potential to benefit [in terms of quality-adjusted life years].

6.10. The Committee considered the original application, the resubmission and all supporting materials that had been submitted, including updated material received since the time of the Rare Disorders Subcommittee.

6.11. The Committee reprised the pathophysiology of SMA and noted that SMA represents a continuous spectrum of phenotypes that are categorised into SMA type based on clinical manifestations i.e. age of symptom onset and motor milestones achieved.

6.12. The Committee noted that the Supplier was not seeking funding of SMA type 0, and that the funding application was specifically for pre-symptomatic and symptomatic patients with SMA type I, II and IIIa who meet specific eligibility criteria.

6.13. The Committee noted that the phenotypic severity and therefore the type of SMA is, at least in part, modified by the number of copies of the SMN2 gene. The Committee noted that people with 4 or 5 copies of SMN2 generally have a milder clinical trajectory with a normal lifespan; and that those with three or less copy numbers have poorer outcomes.

6.14. The Committee considered the epidemiological approach used by the Supplier to estimate the incidence to be appropriate for the NZ setting; however, it considered that patient numbers could be higher if genetic screening for pre-symptomatic SMA was adopted.

6.15. The Committee considered the published key evidence (ENDEAR (Finkel et al. N Engl J Med. 2017;377:1723-32) and CHERISH (Mercuri et al. N Engl J Med. 2018;378:625-35)) and unpublished evidence provided, including interim results from:

6.15.1. ENDEAR-SHINE presented at the 2019 American Academy of Neurology Annual Meeting (Finkel et al. Interim Report on the Safety and Efficacy of Longer term Treatment with Nusinersen in Infantile onset Spinal Muscular Atrophy (SMA): Updated Results From the SHINE Study (S25.004). Presented at: 2019 American Academy of Neurology Annual Meeting (AAN). May 4 to 10, 2019; Philadelphia, PA.).

6.15.2. NURTURE presented at the 2019 Annual Spinal Muscular Atrophy Researcher Meeting (Parsons et al. Nusinersen in Infants Who Initiate Treatment in a Presymptomatic Stage of Spinal Muscular Atrophy (SMA): Interim Efficacy and

Safety Results From the Phase 2 NURTURE Study (S25.001). June 30th 2019. 23rd Annual Spinal Muscular Atrophy Researcher Meeting, 28 to 30 June 2019, Anaheim, CA).

6.15.3. CHERISH-SHINE presented at the 2019 American Academy of Neurology Annual Meeting (Darras et al. Interim Report on the Safety and Efficacy of Longer term Treatment With Nusinersen in Later onset Spinal Muscular Atrophy (SMA): Results From the SHINE Study (P1.6-063). Presented at: 71st American Academy of Neurology (AAN) Meeting. May 4 to 10, 2019; Philadelphia, PA.).

6.16. Based on the evidence (published and unpublished), the Committee considered that, in summary, patients with pre-symptomatic disease (with either 2 or 3 copies) have the largest magnitude of clinical benefit in terms of life years and quality-adjusted life years gained, but also considered that although the effect size is not as great in the symptomatic population in terms of overall and quality-adjusted survival gains, the improvements seen would still be clinically meaningful.

6.17. The Committee considered that although the results [of the trials noted above] are not yet published, and their durations of follow up was limited to date to less than four years, the updated data provided some assurance that the treatment response and large magnitude of effect size was sufficiently persistent and durable to make a recommendation or funding.

6.18. The Committee considered that, based on the evidence reviewed, nusinersen does not cure SMA but likely shifts the severity profile towards a milder disease phenotype. The Committee considered that the evidence supported the assumption that Type I severity is likely to shift to that of a type IIIa severity, but there was uncertainty around whether Type II severity shifts to a IIIa or a IIIb phenotype. Furthermore, the Committee considered that due to the short duration of the data reported to date, it was uncertain that there would be 100% disease re-categorisation of phenotypes to milder phenotypes and considered that assuming so would be an optimistic assumption. The Committee considered that some sensitivity analysis could be modelled to adjust for this area of uncertainty but considered that given the very high price of nusinersen it was unlikely to make a significant improvement to the cost-effectiveness of the treatment.

6.19. The Committee considered the price of treatment was very high resulting in poor cost-effectiveness, and that even if optimistic assumptions around effect size were used, a significant price reduction would need to occur to improve the cost-effectiveness of the application.

6.20. The Committee noted that the Pharmaceutical Benefits Advisory Committee of Australia (PBAC) had recently (Nov 2019) considered funding of nusinersen for the treatment of pre-symptomatic SMA and did not recommend funding for this patient group. In addition, the Committee noted that the PBAC had considered that it may be possible to restrict any future listing of nusinersen for the pre-symptomatic group for patients with ≤2 copies of SMN2.

6.21. The Committee considered information from the Medical Services Advisory Committee of Australia (MSAC) provided to PBAC on the estimated prognostic value of the number of copies of the SMN2 gene for the severity of SMA (MSAC public Summary Document August 2019). The Committee also considered PHARMAC's estimates, based on the MSAC report, of the proportion of SMA patients who would be eligible for pre-symptomatic treatment based on the positive predictive and negative predictive values SMN2 copy number threshold of 3 or less copy numbers, and of 2 or less copy numbers.

6.22. The Committee considered that in simple terms, PHARMAC's estimates mean that if pre-symptomatic eligibility was based on 3 or less SMN2 copies, this would result in at least 1 patient every 3 years in New Zealand who would receive lifelong treatment with nusinersen who would otherwise never have met the proposed eligibility criteria for

symptomatic SMA. If pre-symptomatic eligibility was based on 2 or less SMN2 copies then this would result in at least 1 patient every 30 years who would otherwise never meet the eligibility criteria for symptomatic SMA. However, the Committee considered that the threshold of 3 or less copy numbers would result in a greater number of true positive results (4.6 patients per year would be treated before the onset of symptoms) than if the threshold was ≤2 (1.6 individuals per year would be treated before the onset of symptoms); and that based on the available evidence that treatment is most effective if used early in disease, the Committee was supportive of a funding restriction to those with 2 or 3 copy numbers.

6.23. The Committee noted that there were two other treatments for SMA on the horizon; onasemnogene abeparvovec (a gene therapy treatment, reported publicly to cost upwards of US$2million per treatment) and risdiplam (an oral treatment). The Committee considered that if either of these agents (or both) were to be funded in future that the comparator of lifelong supportive care until death (at times very early) would change.

6.24. The Committee considered the high health need of both populations (pre-symptomatic and symptomatic SMA type I,II and IIIa), and considered that although there was indicative evidence that the pre-symptomatic population were most likely to benefit from treatment (in terms of overall and quality-adjusted survival gains), that the symptomatic group represent the prevalent pool of patients, currently in the care of the health system, and that this group still has the potential for clinically meaningful improvement. The Committee considered that this could, include health benefit to families/whanau caring for children.

6.25. The Committee considered that from a practical point of view it would be difficult for clinicians not to be able to offer treatment for patients who are currently in their care, should pre-symptomatic patients i.e. those not born yet, receive access to funded treatment.

6.26. The Committee considered that, in theory, treating pre-symptomatic patients could mean that numbers of symptomatic patients decline over time.

6.27. The Committee considered there would be a significant cost to the health system should newborn screening be implemented to identify pre-symptomatic SMA patients. The Committee considered that the additional cost of adding SMA to the Newborn Metabolic Screening Programme (Guthrie testing) needed to be quantified and included in the economic and financial analysis of the funding application.

6.28. The Committee considered that supportive care, the treatment comparator, as detailed in the funding application and the clinical trials did not represent the supportive care model of the New Zealand Health system, and that this should be modified in the economic model to be reflective of current practice within the New Zealand Health system.

6.29. The Committee considered that currently supportive care for SMA patients in New Zealand requiring respiratory support generally does not include invasive assisted permanent ventilation e.g. intubation, tracheostomy.

6.30. The Committee considered that if the New Zealand Health System were to start providing invasive assisted permanent ventilation for patients with SMA, that this would be a significant expense to the health sector and would have a large impact on health system resource.

6.31. The Committee considered that, historically, supportive care for patients in NZ with SMA requiring respiratory support has not traditionally included support from a paediatric intensive care unit; however, recently there has been a desire from primary care teams (e.g., neurology or respiratory services) to provide this level of support, partly in an effort to improve current poor survival times and partly with the hope that a treatment for SMA might be funded in the future.

6.32. The Committee considered that SMA patients requiring respiratory support, for intercurrent illnesses, in New Zealand are treated by paediatric intensive care units with non-invasive assisted ventilation support. The Committee considered that, for this reason, the proposed Special Authority criteria should reflect this with regards to measuring ongoing clinical benefit with treatment.

6.33. The Committee considered that it should be possible for clinicians to identify if patients are beginning to stop responding to treatment before the proposed Special Authority renewal (stopping) criteria (including requiring non-invasive permanent assisted ventilation support) are reached.

6.34. The Committee considered using the following age-appropriate scales: the Hammersmith Infant Neuromuscular Examination (HINE) Section 2, the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) or Hammersmith Functional Motor Scale-Expanded (HFMSE) were appropriate scales for assessing motor function as per the proposed Special Authority criteria.

6.35. The Committee considered that the costs of providing paediatric intensive care support for patients requiring respiratory support needed to be included in the financial and economic analysis for the application; and that the costs derived from a German population, as cited in the application, were likely to be substantially lower than that in the New Zealand Health system.

6.36. The Committee considered that, based on the epidemiological information provided, Māori did not appear to be disproportionately affected by SMA compared with the European population; however, the Committee considered that it was difficult to comment on this aspect given small patient numbers.

6.37. The Committee noted that, for historical reasons, oncology paediatric patients have a different funding pathway for access to treatments compared with children with other serious illnesses and with adult patients. The Committee noted that nusinersen was not an oncology treatment and therefore considered it appropriate to consider nusinersen alongside all other pharmaceutical funding applications.

7. TOBI Podhaler (tobramycin dry powder for inhalation) for the treatment of *Pseudomonas aeruginosa* infection in cystic fibrosis patients

Application

7.1. The Committee reviewed an application from Cystic Fibrosis New Zealand for TOBI Podhaler in the treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis.

7.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

7.3. The Committee recommended that TOBI Podhaler be listed as cost neutral to the TOBI inhalation solution, accounting for any offsets to the health sector.

7.4. In making this recommendation, the Committee considered that improvements in quality of life associated with the TOBI Podhaler compared with the nebulised tobramycin solution were primarily due to reduced treatment burden, and increased treatment satisfaction and patient preference. The Committee considered however that there is a lack of evidence to support substantial improvements in adherence and other important health outcomes.

Discussion

7.5. The Committee noted that the Respiratory Subcommittee of PTAC reviewed a supplier application for both the nebulised tobramycin solution for inhalation, TOBI inhalation solution (TIS), and tobramycin dry powder for inhalation (TOBI Podhaler) in April 2014 and had recommended funding both TOBI inhalation solution and TOBI Podhaler under the current access restriction (endorsement) if cost neutral to the tobramycin IV preparation at a dose of 160 mg twice daily. The Subcommittee also recommended funding both the TOBI inhalation solution and the TOBI Podhaler with a medium priority under Special Authority for patients who have had an adverse reaction to the IV tobramycin.

7.6. The Committee considered the new application from Cystic Fibrosis New Zealand for TOBI Podhaler, and noted that the application did not provide any new efficacy evidence not already considered by the Respiratory Subcommittee in 2014.

7.7. The Committee noted that the TOBI Podhaler has Medsafe approval, but that it is not currently supplied or marketed in New Zealand.

7.8. The Committee noted that the Pharmaceutical Benefits Advisory Committee in Australia, Scottish Medicines Commission, The National Institute for Healthcare and Excellence (England/Wales), and the Canadian Agency for Drugs and Technologies in Health had all recommended funding of TOBI Podhaler.

7.9. The Committee noted the Cystic Fibrosis Panel advice of January 2020. The panel considered that the TOBI Podhaler had comparable efficacy to TIS, would reduce the treatment burden, and would result in less bacterial contamination compared to nebulised TIS.

7.10. The Committee considered that PHARMAC's estimate of the size of the cystic fibrosis (CF) population with chronic *Pseudomonas aeruginosa* (*Psa*) infection was reflective of the 2015 Port CF NZ Registry data, which reported the prevalence of cystic fibrosis at 449 with approximately one-third of patients having documented evidence of *Psa* infection, and considered that this was consistent with 2018 dispensing data for the TOBI nebulised inhalation solution (TIS).

7.11. The Committee considered that patients with cystic fibrosis and *Psa* infection have a high health need due to the high treatment burden, significant morbidity and mortality, high rates of acute pulmonary exacerbations and subsequent hospitalisations for prolonged courses of intravenous antibiotics, and potential lung transplantation.

7.12. The Committee considered that the sub-population with the greatest health need is children aged less than 12 years. The Committee noted the significant impact of cystic fibrosis with *Psa* infection on the family/whānau and the health system, and acknowledged the increased rates of parental depression and anxiety and, and substantial parental/caregiver treatment burden associated with caring for children with cystic fibrosis.

7.13. The Committee also noted that in New Zealand, approximately 20% of the total hospitalisations occur in Māori patients, and that this was disproportionate to the relative incidence of cystic fibrosis in Māori in New Zealand, suggesting higher case-morbidity rates.

7.14. The Committee noted that the proposed comparator (TIS) is not always used in this setting as indicated on the Medsafe datasheet. Instead of ongoing treatment in a 28-days-on/ 28-days-off cycle as indicated in the datasheet, the Committee understood that TIS may be used as a two-to-three month course over the winter months, or continuously for some patients. The Committee considered that this usage pattern would likely be no different for the TOBI Podhaler.

7.15. The Committee considered that the proposed use of the same dosing regimen for all patients, independent of age or weight, was potentially problematic.

7.16. The Committee discussed the problems innate to nebulised therapy, noting that the hygroscopic properties of nebulised TIS may be associated with less deposition of drug into the peripheral airways compared to the TOBI Podhaler (Geller et al. J Aerosol Med Pulm Drug Deliv. 2011;24:175-182). The Committee noted that TIS also requires refrigerated storage; in comparison, the TOBI Podhaler has an extended shelf-life at room temperature, is portable and does not require an electrical source, reducing treatment burden compared with the nebulised TIS.

7.17. The Committee noted that patients with cystic fibrosis and chronic *Psa* infection often require nebulised bronchodilators, mucolytics, hypertonic saline, intravenous antibiotics, pancreatic enzymes, vitamins, nutritional supplements, and chest physiotherapy. The committee considered quality of life results from a longitudinal study of adults with cystic fibrosis, reporting that patients usually spend 2-3 hours per day carrying out their treatment regimens (Sawicki et al. J Cyst Fibros. 2009;10:91-6). The Committee considered that nebulised tobramycin was only one of multiple therapies for these patients, and thus had limited incremental impact on the overall time burden of cystic fibrosis therapy. The Committee considered the EAGER study, an open-label study in which 553 patients were randomised 3:2 to TOBI Podhaler or TIS twice daily for three treatment cycles (28 days on-drug, 28 days off-drug), in which the mean duration of drug administration with TOBI Podhaler was significantly less than the inhalation solution and equated to approximately 15 minutes of time saved per use, or 30 minutes per day (Konstan et al. J Cyst Fibros. 2011;10:54-61).

7.18. The Committee considered that nebulisers are more likely to be contaminated with bacteria and fungi due to difficulties associated with cleaning nebulisers, which can also be time-consuming and add to the overall treatment burden. The Committee considered an open-label, crossover, interventional phase IV study in cystic fibrosis patients aged ⩾6 years, in which significantly more devices in the TOBI inhalation solution group were contaminated with bacteria and fungi than those in the TOBI Podhaler group (Greenwood et al. Ther Adv Respir Dis. 2017;11:249-60). The Committee considered that there was no evidence that this resulted in any increased risk of re-infection for cystic fibrosis patients, but noted that in patients with chronic obstructive pulmonary disease this was a substantial risk factor for exacerbations.

7.19. The Committee noted that risk factors for development of multi-drug resistant *Psa* include CF-related diabetes, frequent antibiotic courses, and repeated hospitalisations. Long-term tobramycin administration is also a risk factor, however, the Committee found it was not possible to assess if use of the TOBI Podhaler may increase the likelihood of eradicating *Psa* due to improved adherence and improved intrapulmonary deposition or whether it may inadvertently increase the likelihood of development of multi-drug resistant *Psa* through increased adherence.

7.20. The Committee noted the input from the cystic fibrosis panel that described the comparable efficacy, reduced treatment burden, reduced bacterial contamination and improved treatment adherence of the TOBI Podhaler compared to the TOBI inhalation solution. The Committee agreed with the panel's view that there would be patients who would not be able to use the TOBI Podhaler due to difficulties generating sufficient inspiratory flow, incoordination and the presence of cough. The committee considered that approximately 20-30% of patients would still require access to the TOBI inhalation solution if the TOBI Podhaler were funded.

7.21. The Committee noted that in a retrospective survey in a small number of adults, 75% of patients over 12 months reported they required no intravenous antibiotics during treatment with TOBI Podhaler, which was significantly better than had occurred in the 12 months prior to baseline with the use of the TOBI inhalation solution (44%) (Harrison et al. J Cyst Fibros. 2014;13(6):692-8). However, the committee considered that the evidence for an efficacy benefit for TOBI Podhaler over the TOBI inhalation solution was of low quality because the comparator was retrospective (including time-dependent differential recall bias), and the sample was small (N=78).

7.22. The Committee also noted that the Harrison et al. 2014 study had patients self-reporting improved adherence in the 12 months when using the TOBI Podhaler, compared with when using the TOBI inhalation solution prior to baseline. The Committee considered this result was consistent with another similar retrospective observational follow-up study that reported increased adherence to TOBI Podhaler compared with the TOBI inhalation solution (Blasi et al. Resp Med. 2018;88-94). The Committee considered that while it had been reported that improved adherence to tobramycin inhalation solution was associated with reduced risk of hospitalisations in another retrospective observational follow-up study (Briesacher et al. BMC Pulm Med. 2011;11:5), there was no published evidence of improved adherence and reduced hospitalisation rates with the TOBI Podhaler compared to the TOBI inhalation solution.

7.23. The Committee noted again the results of the EAGER study (Konstan et al. 2011, above), which described an increased rate of cough in the TOBI Podhaler group than the TOBI inhalation solution and that this reduced over time. The Committee considered that in this study, the discontinuation rates were higher in patients randomised to the TOBI Podhaler compared to the TOBI inhalation solution (26.9% vs 18.2%). Members noted that a key driver for the increased discontinuation rates may have been the increased incidence of cough.

7.24. The Committee considered that the main improvement with the TOBI Podhaler compared with the TOBI inhalation solution was in patient satisfaction and preference, due to the reduced treatment burden, and cited the results of the EAGER trial and the Greenwood et al study as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM) and the Chronic Treatment Acceptance Questionnaire (ACCEPT). The Committee considered that these patient satisfaction were largely driven by the reduced time burden for the TOBI Podhaler compared with the TOBI inhalation solution (Konstan et al. 2011; Greenwood 2017).

7.25. The Committee noted the significant price difference between the TOBI Podhaler and the TOBI inhalation solution. The Committee considered that, despite the high need for inhaled tobramycin in this clinical setting, the price differential between the two delivery systems was disproportionately large, and that the price premium was difficult to reconcile with the modest incremental value of the TOBI Podhaler in comparison with the TOBI inhalation solution.
