PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

Level 9, 40 Mercer Street, PO Box 10-254, Wellington 6143, New Zealand

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 16 February & 17 February 2023

This meeting was held in person and via Zoom

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1. Present:

PTAC members:
Jane Thomas (Chair)
Rhiannon Braund (Deputy Chair)
Alan Fraser
Brian Anderson
Bruce King
Elizabeth Dennett
Giles Newton Howes
Jennifer Martin
Lisa Stamp
Matthew Strother
Stephen Munn

Apologies:
Simon Wynn Thomas

2. The role of PTAC, Specialist Advisory Committees and meeting records

2.1. This meeting record of PTAC is published in accordance with the Pharmacology and Therapeutics Advisory Committee (PTAC) Terms of Reference 2021, and Specialist Advisory Committees Terms of Reference 2021.

2.2. The PTAC Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC and Specialist Advisory Committees.

2.3. Conflicts of Interest are described and managed in accordance with sections 6.4 of both the PTAC Terms of Reference and Specialist Advisory Committee Terms of Reference.

2.4. PTAC and Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. PTAC may therefore, at times, make recommendations that differ from Specialist Advisory Committees', including the priority assigned to recommendations, when considering the same evidence. Likewise, Specialist Advisory Committees may, at times, make recommendations that differ from PTAC's, or from other Specialist Advisory Committees', when considering the same evidence.

Pharmac considers the recommendations provided by both PTAC and Specialist Advisory Committees when assessing applications.

3. Record of PTAC meeting held 17 November & 18 November 2022

3.1. The Committee reviewed the record of the PTAC meeting held on 17 November & 18 November 2022

3.2. The Committee accepted the record.

4. Specialist Advisory Committee Record

Cardiovascular Advisory Committee meeting June 2022

4.1. The Committee reviewed the record of the Cardiovascular Advisory Committee meeting held on 8 June 2022

4.2. The Committee noted the record.

Gastrointestinal Advisory Committee meeting August 2022

4.3. The Committee reviewed the record of the Gastrointestinal Advisory Committee meeting held on 23 August 2022

4.4. The Committee noted the record.

Cancer Treatments Advisory Committee Ad-hoc meeting October 2022

4.5. The Committee reviewed the record of the Cancer Treatments Advisory Committee Ad-hoc meeting held on 14 October 2022

4.6. The Committee noted the record.

Diabetes Advisory Committee ad hoc dulaglutide meeting October 2022

4.7. The Committee reviewed the record of the Diabetes Advisory Committee ad hoc dulaglutide meeting held on 17 October 2022

4.8. The Committee noted the record.

Endocrinology Advisory Committee meeting August 2022

4.9. The Committee reviewed the record of the Endocrinology Advisory Committee meeting held on 8 August 2022

4.10. The Committee noted the record.

Immunisation Advisory Committee September 2022

4.11. The Committee reviewed the record of the Immunisation Advisory Committee meeting held on 9 September 2023. The Committee noted the recommendations made by the Advisory Committee.

4.12. The Committee specifically noted the Advisory Committee's view that there is a high health need arising from pertussis (whooping cough), with inequity and increased burden for very young infants (especially those less than six months of age). The Committee agreed that there is a significant burden for Māori and Pacific Peoples and considered that it is important to ensure that Māori and Pacific peoples can access immunisation services.

5. Correspondence & Matters Arising

Ustekinumab for Crohn's disease or ulcerative colitis

Application

5.1. The Committee reviewed the application for Ustekinumab for first-line biologic treatment of Crohn's disease and ulcerative colitis.

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** widening access to Ustekinumab to first-line biologic use for those with Crohn's disease or ulcerative colitis with a **low priority** subject to the following Special Authority criteria**:**

USTEKINUMAB
Initiation –Crohn's disease- adult
Applications only from a relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Individual has active Crohn's disease; and
2. Any of the following:
   - 2.1. Patient has Crohn's disease active index (CDAI) score of greater than or equal to 300; or HBI score greater than or equal to 10; or
   - 2.2. Patient has extensive small intestine disease affecting more than 50cm of the small intestine; or
   - 2.3. Patient has evidence of short gut syndrome or would be at risk of short gut syndrome with further bowel resection; or
   - 2.4. Patient has an ileostomy or colostomy and has intestinal inflammation; and
3. Any of the following:
   - 3.1. Patient has tried but had experienced an inadequate response to (including lack of initial response and/or loss of initial response) from prior therapy with immunomodulators and corticosteroids; or
   - 3.2. Patient has experienced intolerable side effects from immunomodulators and corticosteroids; or
   - 3.3. Immunomodulators and corticosteroids are contraindicated.

Renewal –Crohn's disease – adult
Applications only any relevant practitioner. Approvals valid for 2 years.
Both:
1. Either

1.1. CDAI score has reduced by 100 points from the CDAI score when the patient was initiated on biological therapy; or HBI score has reduced by 3 points from when patent was initiated on biological therapy; or
1.2. CDAI score is 150 or less, or HBI is 4 or less; or
1.3. The patient has experienced an adequate response to treatment, but CDAI score cannot be assessed; and

2. Ustekinumab will be used at a dose no greater than 90 mg subcutaneously every 8 weeks.

USTEKINUMAB
Initiation –Crohn's disease- children
Applications only from a relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Individual has active Crohn's disease; and
2. Any of the following:
   2.1. Patient has Paediatric Crohn's disease active index (PCDAI) score of greater than or equal to 30; or
   2.2. Patient has extensive small intestine disease; and
3. Any of the following:
   3.1. Patient has tried but had experienced an inadequate response to (including lack of initial response and/or loss of initial response) from prior therapy with immunomodulators and corticosteroids; or
   3.2. Patient has experienced intolerable side effects from immunomodulators and corticosteroids; or
   3.3. Immunomodulators and corticosteroids are contraindicated; and

Renewal –Crohn's disease – children
Applications only any relevant practitioner. Approvals valid for 2 years.
All of the following:
1. Either
   1.1. PCDAI score has reduced by 10 points from when the patient was initiated on biological therapy; or
   1.2. PCDAI score is 15 or less ;or
   1.3. The patient has experienced an adequate response to treatment, but PCDAI score cannot be assessed; and
2. Ustekinumab will be used at a dose no greater than 90 mg subcutaneously every 8 weeks.

Initiation –ulcerative colitis
Applications from any relevant practitioner. Approvals valid for 6 months for application meeting the following criteria:
All of the following:
1. Patient has histologically confirmed ulcerative colitis; and
2. Any of the following:
   2.1. Patients has a SCCAI core greater than or equal to 4; or
   2.2. Patients PUCAI score is greater than or equal to 20; and
3. Any of the following
   3.1. Patient has tried but had experienced an inadequate response to (including lack of initial response and/or loss of initial response) from prior therapy with immunomodulators and corticosteroids; or
   3.2. Patient has experienced intolerable side effects from immunomodulators and corticosteroids; or
   3.3. Immunomodulators and corticosteroids are contraindicated.

Renewal –ulcerative colitis
Applications from any relevant practitioner. Approvals valid for 2 years for any application meeting the following criteria:
Both
1. Either:
   1.1. The SCCAI score has reduced by 2 points or more from the SCCAI score when the patient was initiated on biological therapy; or
   1.2. The PUCAI score has reduced by 10 points or more from the PUCAI score since initiation on biological therapy; and
2. Ustekinumab will be used at a dose no greater than 90 mg subcutaneously every 8 weeks.

5.4. In making its recommendation the Committee considered that:

- There was good-quality trial evidence in Crohn's disease, which provided moderate strength evidence that rates of response and remission were similar for ustekinumab compared to adalimumab in the short term.

- There was a high health need for those with ulcerative colitis that require first-line biologic treatment.
- Ustekinumab did not need to be co-administered with azathioprine, reducing side effects and pill burden.
- Māori and Pacific peoples may experience inequities during diagnosis.
- That it would like to see additional evidence comparing the different inflammatory bowel disease biologics in different lines of treatment.

Discussion

Māori impact

5.5. The Committee considered that whilst data suggested that Māori and Pacific peoples were under-represented in the Crohn's disease or ulcerative colitis population, it is possible that equity issues including access to healthcare specialists may affect diagnosis, and therefore the current data may not accurately reflect the actual incidence and prevalence of inflammatory bowel disease (IBD) in some populations.

5.6. The Committee noted that few individuals receiving biologic treatment for ulcerative colitis were Māori (6%) or Pacific peoples (1%) (as of 30 June 2021; PharmHouse data).

Background

5.7. The Committee noted that ustekinumab has previously been considered by PTAC for the treatment of Crohn's disease and ulcerative colitis by the Committee in:

- May 2018 – Medium Priority recommendation for the second line treatment of Crohn's disease
- February 2019 – reiterated Medium Priority recommendation for second-line treatment of Crohn's disease
- May 2020 – Medium Priority recommendation for the second-line treatment of ulcerative colitis

5.8. The Committee noted that ustekinumab is currently funded as a second-line biologic for those with Crohn's disease or ulcerative colitis, and that listing it as a first-line biologic would allow clinicians to use ustekinumab at any line of biologic therapy.

Health need

5.9. The Committee noted that historically the crude incidence and prevalence of ulcerative colitis in New Zealand has been estimated to be 7.5 and 145 cases per 100,000 population respectively(Gearry et al. Inflamm Bowel Dis. 2006;12:936-43), whilst in 2014 the estimated age-standardised incidence rate for Crohn's disease was 26.4 per 100,000 (Su et al. Inflamm Bowel Dis 2016;22: 2238-44).

5.10. The Committee noted that there is variability in the presentation of the disease, for example ulcerative colitis presents with continuous areas of inflammation, whilst in Crohn's disease there are areas of healthy tissue between areas of inflammation. The Committee noted that both conditions are associated with a higher mortality and increased likelihood of being diagnosed with cancer.

5.11. The Committee noted that it has previously considered and discussed the high health need of the population during previous considerations of IBD.

Health benefit

5.12. The Committee reviewed data from the SEAVUE trial (Sands et al. Lancet. 2022;399:2200-11), for the treatment of people with moderately to severely active Crohn's disease who are naïve to biologic agents. The Committee noted that the study, a randomised, double-blind, parallel-group trial, was relevant for the New Zealand population regarding comparison to adalimumab, the inclusion criteria of Crohn's disease active index (CDAI) 220-450, and the individuals enrolled in the trial being biologically naïve. The Committee noted that the study indicated that 65% of people in the ustekinumab group versus 61% in the adalimumab group were in clinical remission at week 52 (between-group difference 4%, 95% CI -6 to 14; p=0·42), with similar adverse events. The Committee noted that there were lower rates of treatment discontinuation due to adverse events in the ustekinumab treated population compared to adalimumab (6% vs 11% respectively).

5.13. The Committee noted data from the UNIFI trial (Abreu et al. J Crohns Colitis. 2022;16:1222-34). The Committee noted that this long-term extension study reported data from ustekinumab treatment with 3 years of maintenance in 348 people with ulcerative colitis, as well as a further 284 people who were treated with ustekinumab following unblinding. The Committee noted that in those that were biologic treatment naïve there was persistence of remission, of approximately 70-80%, which the Committee considered was similar to other biologic treatments.

5.14. The Committee also noted the Onali et al. study (Am J Gastroenterol. 2022 1;117:1279-1287), an observational retrospective cohort study indirectly comparing the effectiveness of vedolizumab and ustekinumab in those with Crohn's disease that had progressed despite the use of tumour necrosis factor (TNF)-alpha inhibitors. The Committee noted that this is relevant to the current treatment paradigm in New Zealand following the funding of vedolizumab. The Committee noted that there was no significant difference between the treatments when considering week 6 clinical response (60.1% vs 65.4% ustekinumab, vedolizumab respectively) and week 52 objective remission (29.9% vs 28.4% ustekinumab, vedolizumab respectively).

5.15. The Committee noted a retrospective cohort study by Chien et al (Biologics. 2021; 15:237-245) observing persistence rates for ustekinumab use in Crohn's disease in an Australian population. The Committee noted the study reported that 12-month persistence for those receiving ustekinumab as a monotherapy (81.3%, 95% CI 75.5% to 87.6%) was similar to those receiving ustekinumab as a combination therapy with an immunosuppressant (84.9%; CI 77.8% to 92.6%).

5.16. The Committee noted evidence from an observational study by Barclay et al (Intern Med J. 2019;49:513-518) suggesting that thiopurine co-administration helped to increase response to biologics by supressing anti-drug antibodies (ADA). The Committee noted half of the study population received concomitant immunosuppressants. The Committee considered that clinicians in New Zealand are favouring a reduction in the use of thiopurines due to the associated risk of adverse events.

5.17. The Committee noted evidence (Lemaitre et al, JAMA. 2017;318:1679-86) of an increased risk of lymphoma for individuals with IBD who received anti-TNF therapy in combination with a thiopurine (adjusted HR 3.95, 95% CI 1.01-15.5).

5.18. The Committee also noted a meta-analysis of 13 studies (Huang et al, J Gastroenterol Hepatol. 2019; 34:507-16) reporting an increased risk of skin cancer in people with IBD administered thiopurines (pooled random effects relative risk 1.80, 95% CI 1.14-2.87, p=0.013). The Committee noted that anti-TNF therapies can also increase the risk of skin cancer, and annual skin checks are recommended for this population.

5.19. The Committee also noted the following publications providing evidence for the use of ustekinumab for the treatment of ulcerative colitis or Crohn's disease:

- Ko et al. Aliment Pharmacol Ther. 2021; 54:292-301
- Hanauer et al. J Crohns Colitis. 2020;14:23-32
- Abreu et al, J Crohns Colitis. 2022; 16:1222-1234
- Monin et al, Dig Liver Dis. 2021;53:72-8
- Sedano et al, Inflamm Bowel Dis. 2022 Jul 19;izac149
- Parra et al BMC Gastroenterol. 2022 Apr 21;22:199:
- Wong et al, Inflamm Bowel Dis. 2022 3;izac168
- Riviere et al, Inflamm Bowel Dis. 2022 2;izac167
- Singh et al, Aliment Pharmacol Ther. 2018;48:394-409
- Welty et al, Curr Med Res Opin. 2020;36:595-606
- Lasa et al, Lancet Gastroenterol Hepatol. 2022;7:161-170
- Singh et al, Clin Gastroenterol Hepatol. 2020;18:2179-91.e6

8.21. The Committee considered the evidence to be of moderately high strength and quality with regards to the SEAVUE trial (Sands et al, 2022). The Committee considered that the available evidence did not suggest a benefit of ustekinumab as a first-line induction or maintenance treatment in Crohn's disease compared to adalimumab. The Committee considered that there was less certainty about the comparative effectiveness of ustekinumab versus other treatments in ulcerative colitis, given the lack of head-to-head trial evidence. The Committee considered that meta-analysis evidence suggested ustekinumab was likely to provide a benefit in ulcerative colitis versus other agents, particularly adalimumab, though this benefit was less certain.

5.21. The Committee considered it was likely that ustekinumab would be used as monotherapy for many patients, and that this was likely to result in a reduction in long-term adverse events associated with thiopurine use, including a reduction in risk of developing lymphoma and other cancers. The Committee considered that benefits associated with greater persistence were uncertain given the short duration of the

Suitability

5.22. The Committee noted that ustekinumab can be provided as a monotherapy, reducing the need for thiopurines and consequent side effects. The Committee noted that ustekinumab monotherapy also reduced the need for additional blood testing for thiopurine levels and checks for skin cancer. The Committee noted that currently funded biologic therapies (infliximab, adalimumab and vedolizumab) generally require thiopurine co-administration.

5.23. The Committee noted that ustekinumab as a monotherapy would offer a reduction in pill burden compared to currently funded biologic therapies, which likely require combination therapy.

5.24. The Committee also noted ustekinumab is available as a prefilled syringe for subcutaneous injection, following the first dose which is administered over the course of a 1-hour intravenous infusion in hospital. The Committee noted that, in comparison, infliximab and vedolizumab must be administered via intravenous infusion in an inpatient setting at weeks 0, 2, and 6, and every 8 weeks thereafter. The Committee considered that the subcutaneous route of administration reduced the travel burden to infusion centres in comparison to infliximab and vedolizumab. The Committee also considered that 8-weekly administration offered an advantage to 2-weekly administration of adalimumab.

Cost and savings

5.25. The Committee noted that the subcutaneous dosing route would reduce the burden on infusion centres in comparison with other biologic drugs, and that it was important to consider those costs and effects on health services in the economic analysis.

5.26. The Committee noted that thiopurines concomitantly administered with other biologic therapies would likely result in greater monitoring, including blood tests measuring thiopurine metabolite levels, bone marrow suppression, liver toxicity and annual skin checks. In addition, the Committee considered that there would be a decrease in the number of individuals having severe adverse effects associated with the administration of immunosuppressive therapies, as ustekinumab can be administered as a monotherapy.

5.27. The Committee considered that uptake of ustekinumab in a first-line setting for Crohn's disease was likely to be low, given the familiarity of clinicians with adalimumab as a first-line agent. The Committee considered that uptake was likely to be higher for ulcerative colitis, given that first-line adalimumab is less effective in this setting and other biologics

require intravenous administration. The Committee considered that it was likely the ulcerative colitis first-line uptake was likely to be in excess of the 25% market share estimate made by Pharmac staff.

Summary for assessment

5.28. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ustekinumab if access to ustekinumab were widened to allow use as a first-line biologic treatment for Crohn's disease and ulcerative colitis. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may develop based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with biologic-naïve severe Crohn's disease who have experienced inadequate benefit from prior therapy	Individuals with biologic-naïve moderate-severe UC who have experienced inadequate benefit from prior therapy
Intervention	Ustekinumab, administered as 390mg on day 0, followed by 90mg every 8-12 weeks Ustekinumab may be used either as monotherapy or in combination with azathioprine with likely similar benefit	
Comparator(s) (NZ context)	First-line biologic, assumed to be a combination of: - Adalimumab (~85%) - Vedolizumab (~5%) - Infliximab (~10%) Currently funded first-line biologics typically used in combination with immunosuppressants	First-line biologic, assumed to be a combination of: - Adalimumab (~35%) - Infliximab (~35%) - Vedolizumab (~30%) Currently funded first-line biologics typically used in combination with immunosuppressants
Outcome(s)	Similar rates of remission and response to currently funded agents, based on SEAVUE (Sands et al Lancet, 2022) No evidence of superior persistence compared to other biologic in a first-line setting Reduced need for concomitant immunosuppressants. - Likely to result in fewer adverse events, including lower long-term risk of cancers. - Reduced need for immunosuppressants may be associated with greater persistence	No direct evidence vs other biologic agents Meta-analysis evidence suggests there may be a benefit compared to adalimumab, with less certain benefits vs vedolizumab or infliximab in a first- line setting Likely greater long-term persistence vs other agents, based on maintenance of benefit observed in long-term extension of UNIFI (Abreu et al, J Crohns Colitis, 2022) Reduced need for concomitant immunosuppressants. - Likely to result in fewer adverse events, including lower long-term risk of cancers. - Reduced need for immunosuppressants may be associated with greater persistence
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.		

6. Voretigene neparvovec for the treatment of RPE65-mediated inherited retinal dystrophies

Application

6.1. The Committee reviewed the supplier application for voretigene neparvovec in the treatment of inherited retinal dystrophies caused by pathological biallelic *RPE65* mutations.

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 voretigene neparvovec be **deferred** until further evidence regarding the longevity of the therapeutic benefits becomes available.

6.4. The Committee noted in making this recommendation that data from subsequent follow-ups from the Phase 3 trial cohort, and emerging evidence around treatment effect for gene therapies more generally, would provide greater confidence on the expected duration of the health benefits associated with individuals being treated with voretigene neparvovec.

Discussion

Māori impact

6.5. The Committee noted the impact of funding voretigene neparvovec for the treatment of RPE65-mediated inherited retinal dystrophy (IRD) on Māori health areas of focus and Māori health outcomes. The Committee noted that there is currently one specialist who provides care for all individuals impacted by RPE65-mediated IRD in New Zealand and that there are no reported cases of Māori individuals who are impacted by RPE65-mediated IRD. The Committee noted that there are Māori impacted by IRDs in New Zealand, however a significant proportion of these individuals are living with PDE6b-mediated IRDs, which voretigene neparvovec would not be used to treat. The Committee noted that this does not exclude the possibility that Māori may be impacted by RPE65-mediated IRD, and the absence of current cases may be due to the condition's rarity.

Background

6.6. The Committee noted that the supplier's application for voretigene neparvovec is the first gene therapy to be considered by the Committee. The Committee noted that Pharmac has not previously received a funding application for an inherited retinal dystrophy.

6.7. The Committee noted that inherited retinal dystrophies are a group of genetically and phenotypical heterogenous diseases that result in the progressive loss of photoreceptor function and eventual irreversible blindness. The Committee noted that *RPE65* is involved in the regulation of light responsive pigment in the retina and abnormal *RPE65* leads to malfunctioning rod photoreceptors and eventual permanent damage of the retinal epithelial cells. This results in night blindness, deterioration of visual acuity and progressive eventual blindness.

6.8. The Committee noted that a *RPE65*-mediated IRD diagnosis is made when two abnormal copies of the gene (these can be different variants) are present. The Committee noted that there have been over 60 different mutations in the *RPE65* genes reported, and that the heterogenicity of the mutations and the subsequent impact on RPE65's functional properties accounts for the range of phenotypes presented by the individuals. The Committee noted that abnormalities in the *RPE65* gene is implicated in two main clinical conditions: Leber congenital amaurosis, and retinitis pigmentosa.

Health need

6.9. The Committee noted that there is an unmet health need for individuals with *RPE65*-mediated IRD due to there being no treatments currently available in New Zealand.

6.10. The Committee considered the health need is high as individuals generally present with symptoms before the age of five and their vision will continue to decline as they age. The Committee noted that individuals diagnosed with Leber congenital amaurosis or retinitis pigmentosa typically become legally blind by the age of 20 and 40, respectively.

6.11. The Committee noted that losing visual acuity at an early age has wide-ranging implications for an individual's social position, education, mental health, and general

health (Cumberland & Rahi. JAMA Ophthalmol. 2016; 134:959-66). The Committee noted that the overall health need is difficult to quantify, and the impact of vision loss experienced by the individual can be variable. The Committee noted that the evidence regarding the health need associated with *RPE65*-mediated IRD was limited due to the rarity of the disease

6.12. The Committee noted that retinitis pigmentosa affects an estimated 1 in 4000 people and 3% of these individuals' sight is affected by mutations in the *RPE65* gene. The Committee noted that Leber congential amaurosis affects an estimated 1 in 80,000 people and 10% of these individuals' sight is affected by mutations in the *RPE65* gene (Sallum et al. Adv Ther. 2022; 39: 1179-98).

6.13. The Committee noted the *RPE65* is the probable causative agent for three families with clinically diagnosed IRD in New Zealand (Hull et al. Am J Med Genet C Semin Med Genet. 2020; 184:708-717). The Committee considered the applicant's estimated number of 13 people affected to be speculative, but not unrealistic, as only child-onset IRD have been reported in New Zealand and that some individuals may not be able to access the appropriate health care options to be considered for genetic diagnosis.

6.14. The Committee noted that Māori and Pacific peoples have been diagnosed with *PDE6b*-mediated IRDs. The Committee noted that no individuals living with IRDs and genetically tested for the *RPE65* mutation are reported to be of Māori or Pacific ethnicity. The Committee noted that it was unknown if Māori or Pacific peoples were disproportionally impacted by *RPE65*-mediated IRD due to lack of evidence and the rarity of the disease.

6.15. The Committee considered that the health needs and emotional distress of families and whānau of individuals with *RPE65*-mediated IRDs would be significant.

Health benefit

6.16. The Committee noted that voretigene neparvovec is an adeno-associated viral type 2 gene therapy vector with a cytomegalovirus enhancer and chicken beta actin promoter driving the expression of the functional human retinal pigment epithelium 65 kDa protein (h*RPE65*) gene. Voretigene neparvovec is designed to deliver a functional copy of human *RPE65* gene to the cells of the retina (retinal pigment epithelial cell) in individuals who have reduced or absent levels of biologically active RPE65. Cellular response to the provision of the biologically active RPE65 results in corrected cycling of the visual cycle (retinoid cycle)

6.17. The Committee noted that the risks documented with voretigene neparvovec as an intervention have been those associated with retinal eye surgery and sub-retinal injection and are outlined in 9.19.1.2 below.

6.18. The Committee considered the following evidence relating to the use of voretigene neparvovec in the treatment of *RPE65*-mediated IRD:

- Russell et al. Lancet. 2017; 390:849-60: A randomised, open label trial of individuals 3 years or older with confirmed RPE65-mediated IRD with sufficient viable retinal cells and with visual acuity of 20/60 or worse or visual fields less than 20 degrees in any meridian or both. 20 individuals received a subretinal injection of 1.5 x 1011 vector genomes voretigene neparvovec in a total subretinal volume of 0.3mL delivered to the first assigned eye, and after 6-18 days the second eye was treated. Nine individuals were in the control group and these individuals received voretigene neparvovec after the conclusion of the study at 1-year.

- Individuals visual function was assessed before and after therapeutic intervention (if received), with initial base line results compared to 1-year follow-up results to determine change in vision function. Individuals who received voretigene neparvovec demonstrated an average improvement of 1.8 (SD 1.1) in the bilateral multi-luminance mobility test compared to the control group 0.2 (SD 1.0). After 30 days difference in change of score of 1.6 (95% CI 0.72 to 2.41, p= 0.0013) between voretigene neparvovec and control group was noted. The groups maintained the change throughout the first year in the bilateral multi-luminance mobility test. At 1-year, 65% of intervention group passed the bilateral multi-luminance mobility test at the lowest level of luminescence vs 0% in the control group. Individuals who received voretigene neparvovec experienced improvement in light sensitivity from day 30 following treatment and this was maintained through 1-year of monitoring. The intervention group gained 8.1 letters in the Holladay scale of the visual acuity test in comparison to the control groups gain of 1.6 letters. The intervention group gained 9 letters in the Lange scale of the visual acuity test in comparison to the control groups gain of 1.6 letters. The intervention group gained 302 degrees and the control group lost 76.7 degrees in visual field testing. The intervention group gained 7.7 decibels and the control group lost 0.2 decibels in macular threshold testing. A mean change of 7.9 decibels (95% CI 3.50 to 12.2, p=0.0005) No meaningful change was demonstrated in either group in comparison to pre-injection foveal sensitivity measurements.

- No severe adverse effects were reported. Moderate events included eye irritation (5%), eye pruritus' (5%) retinal tear (10%), macular hole/degeneration (5%). Mild events included elevated intraocular pressure (20%), cataract (15%), eye inflammation (10%), conjunctival cyst (5%), conjunctivitis viral (5%), eye pain (5%), eye swelling (5%), foreign body sensation in eye (5%), iritis (5%), maculopathy/epiretinal membrane (5%), pseudopapolledema (5%), and retinal haemorrhage (5%).

- Maguire et al. Ophthalmology. 2021; 128:1460-1468:

6.19. A follow-up of the trial by Russell et al. (2017) to assess the durability of voretigene neparvovec following intervention 3 and 4 years prior. Previously reported results in regard to the bilateral multi-luminance mobility test and light sensitivity improvements assessed in Russell et al. Lancet. 2017; 390:849-60 remained stable at year 3 and 4. The visual acuity improvements were maintained for years 1-3 however by year 4 the visual acuity scores had reverted to the pre-injection levels. Over 30% of patients had maintained clinically meaningful improvements from baseline. In regard to visual field testing, the improvements declined at year 4 of monitoring, however they had still improved in regard to the pre-injection levels.

6.20. The Committee noted the following evidence included in the application:

- Maguire et al. Lancet. 2009; 374:1597-605
- Testa et al. Ophthalmology. 2013; 120:1283-91
- Bennet et al. Lancet. 2016; 388:661-72
- Testa et al. Sci Reps. 2022; 12:17637
- Gange et al. Ophthal Retina. 2022; 6:58-64

6.21. The Committee noted that the trials included small numbers of participants but considered that this was not unexpected due to the rarity of the disease. The Committee considered that the evidence was of good quality due to the robust design and multiple measurements done to confer results.

6.22. The Committee considered that there was no obvious endpoint that could be used to define 'successful treatment' with voretigene neparvovec given the range of endpoints reported in trials and uncertainty around how changes to these endpoints translate into improvements in health-related quality of life. The Committee considered that greater clarity around the clinical meaningfulness of these endpoints would be needed before a determination regarding successful treatment could be made. The Committee considered that the health benefits reported in the trials are likely to be beneficial for family and whānau in addition to the individual receiving treatment.

6.23. The Committee noted that a key uncertainty in the benefit derived from voretigene neparvovec treatment was the duration of treatment effect, which refers to the period over which an individual accrues some, or all, of the potential benefit from treatment. The Committee considered that, based on the available trial evidence, it was reasonable to assume a treatment effect of at least three years, with waning or no treatment benefit thereafter.

6.24. The Committee considered that a duration of treatment effect of greater than three years was biologically plausible, and Committee noted that retinal cells are a terminally differentiated, non-replicating, cell type which could reasonably be expected to retain episomes of healthy copies *RPE65* after successful delivery via voretigene neparvovec. The Committee noted evidence that in animal studies of voretigene neparvovec, episomes with healthy copies of the *RPE65* gene were found in the target cell types as long as 10 years after injection (Leroy et al. Opthalmic Res. 2022 [preprint]). The Committee considered however that if a substantial proportion of retinal cells were not covered by the injection site, some deterioration of vision could occur even after initially successful treatment.

6.25. The Committee noted that the standard of evidence required to support assumption of treatment effects beyond three years duration in humans was not yet available. The Committee noted that over the four-year follow-up period of Russell et al. Lancet. 2017; 390:849-60, there was early evidence of a waning treatment benefit in year 4 after voretigene neparvovec administration (Maquire et al. Ophthalmology. 2021; 128:1460-1468). The Committee considered that data from subsequent follow-up studies of the Russell et al. Lancet. 2017; 390:849-60 cohort, and emerging evidence around treatment effect for gene therapies more generally, would provide greater confidence on the expected duration of treatment benefit associated with voretigene neparvovec.

6.26. The Committee considered that voretigene neparvovec prevents further vision loss but does not improve vision. The Committee considered that voretigene neparvovec would therefore benefit those individuals who have a sufficient number of healthy retinal cells and that immediate intervention with voretigene neparvovec following confirmed *RPE65*-mediated IRD would be the most appropriate to prevent further vision loss.

6.27. The Committee noted that it is unknown whether an individual could receive additional courses of voretigene neparvovec due to the irreversible and progressive loss of vision associated with *RPE65*-mediated IRD.

6.28. The Committee considered that there would be considerable consequences for the health system if voretigene neparvovec were to be funded. The Committee noted that voretigene neparvovec must be prepared in a pharmaceutical compounding setting that is capable of handling and preparing adeno-associated viral vector-based gene therapy products and considered that such a setting may not currently be available in New Zealand. The Committee considered that significant upskilling and training of involved personnel would be required to implement this service.

6.29. The Committee noted that the supplier reported that a treatment centre would require an ophthalmologist with expertise in the care and treatment of people with IRDs, along with the presence of, or an affiliation with, a retinal surgeon experienced in sub-retinal surgery and capable of administrating voretigene neparvovec. The Committee noted that this therapy is extremely specialised, and that considerable effort would be required to provide the appropriate clinical setting.

Suitability

6.30. The Committee noted that voretigene neparvovec is injected into each eye separately, with a minimum of 6-days between each injection and that individuals receiving this therapy would be required to travel twice to the treatment centre to receive this therapy. The Committee noted that there is currently no facility that is immediately able to store, prepare, handle, and administer the therapy The Committee considered that the most likely location for such a facility would be in Auckland where there is an IRD specialist clinic. However, the Committee considered that this may be an additional barrier for people who live rurally, or who must take extended trips to visit the centre where the treatment is available.

Cost and savings.

6.31. The Committee noted that, based on international epidemiological data, there were potentially as many as 13 people with RPE65-mediated IRDs in New Zealand and that to date, three individuals have been identified through testing. The Committee noted that the supplier estimated that 55% of these individuals would have sufficient viable retinal cells to be eligible for voretigene neparvovec The Committee considered that testing rates for RPE65 mutations and the uptake rate for voretigene neparvovec among eligible individuals could be as high as 100% if voretigene neparvovec was funded, given the lack of funded alternative treatments for IRDs, regardless of the need for travel to receive treatment.

6.32. The Committee considered that funding voretigene neparvovec could result in incremental costs to the health system due to requirements around testing for eligibility for treatment, and the protocols and infrastructure required to deliver this gene therapy. The Committee considered that there would also likely be training requirements for clinicians involved in the administration of voretigene neparvovec into the subretinal space. The Committee considered, however, that the numbers of treatments delivered would to be small given the small numbers of eligible individuals with RPE65-mediated IRDs.

6.33. The Committee noted the challenges associated with appraising the value of gene therapies due to the high pharmaceutical costs, the substantial uncertainty in the duration of treatment effect, the health-related quality of life benefits, and the potential need for re-treatment if the treatment effect waned. The Committee considered that the cost-effectiveness of voretigene neparvovec was likely to be influenced by these factors and was also highly uncertain given the lack of longer-term follow-up data to date.

Summary for assessment

6.34. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for voretigene neparvovec if it were to be funded in New Zealand for the treatment of RPE65-mediated IRD. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with inherited retinal dystrophy due to pathological biallelic mutations of the *RPE65* gene, with sufficient viable retinal cells.
Intervention	Voretigene neparvovec, administered once as a subretinal injection in each eye in combination with peri-procedural treatment with prednisone.
Comparator(s)	Best supportive care
Outcome(s)	Reduced visual decline. • Russell et al. Lancet. 2017;390: 849-860 reported that voretigene neparvovec treatment is associated with an improvement in LogMAR score compared to placebo at 1-year post-treatment (mean difference -0.16, 95% CI = -0.41 to 0.08). • The long-term duration of such benefits is uncertain. Reduced vision impairment (i.e., improved LogMAR score) is associated with improvements in health-related quality of life (Lloyd et al. BMJ. 2019;103: 1610-1614)
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

7. Rotigotine patches for Parkinson's disease

Application

7.1. The Committee reviewed the application for rotigotine in the treatment of Parkinson's disease

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** rotigotine for Parkinson's disease be listed as **cost-neutral** to other funded non-ergot dopamine agonists (pramipexole or ropinirole).

7.4. The Committee considered the following reasons for this recommendation:

- Rotigotine is non-inferior to other dopamine agonists currently funded (pramipexole or ropinirole) and funding of this proposal would provide an additional option for non-ergot dopamine agonist treatment in Parkinson's disease with an alternative formulation
- Rotigotine has been associated with decreased risks of impulse control disorders, a rare adverse event. Due to the rarity of this event, the potential magnitude of this benefit was not sufficient to suggest a significant benefit over other currently funded non-ergot dopamine agonists. Additionally, rotigotine is associated with a greater risk of adverse events overall compared to other non-ergot dopamine agonists.
- Within the non-ergot dopamine agonists class, there are two funded alternatives (pramipexole and ropinirole), and there are other funded alternatives for treatment of Parkinson's disease in other classes

7.5. The Committee considered that Pharmac staff could see further advice regarding rotigotine for Parkinson's disease from the Neurological Advisory Committee regarding:

- Whether there are subgroups within the Parkinson's disease indication which have a different health need to the general Parkinson's disease population or would benefit from rotigotine such as, but not limited to, those people unable to take oral medications acutely or otherwise, those with morning off-time, with sleep disturbance, dementia or other non-motor symptoms.

Discussion

Māori impact

7.6. The Committee discussed the impact of funding rotigotine patches for the treatment of Parkinson's disease on Māori health areas of focus and Māori health outcomes. The Committee noted that the reported incidence of Parkinson's disease in Māori was less than in people of European decent (Pitcher et al. Mov Disord. 2018;33:1440-48). The Committee considered this may be due to an inequity in access to diagnostic specialist services for Māori and Pacific peoples, but unfortunately this potential confounding was unquantifiable at this time.

Background

7.7. The Committee noted that a supplier application for rotigotine patches was previously considered by PTAC in 2014 and received a cost-neutral recommendation (to pramipexole or ropinirole). The Committee noted that this application was formally declined in March 2022 due to cost-neutrality not being reached.

7.8. The Committee noted that the application being considered at this meeting was a clinician application for rotigotine patches for Parkinson's disease and that this application included Parkinson's disease-related evidence published since PTAC's previous consideration of rotigotine. The Committee noted that application had three general indications including early Parkinson's disease, advanced Parkinson's disease and those unable to take oral medicines.

7.9. The Committee noted that Parkinson's disease is a progressive disease with a relapsing-remitting nature, due to the loss of dopaminergic neurons, impacting motor function and resulting in 'on-off periods'. The Committee noted that most treatments are focussed on reducing the motor off periods while balancing the risk of toxicity or side effects, which include augmentation (a hyperkinetic period followed by a period of relative motor normalcy and then a hypokinetic period). The Committee noted that there are also other non-motor components to Parkinson's disease including sleep disturbance, depression and anxiety.

7.10. The Committee considered that for Parkinson's disease there are a number of funded medicines within each class of treatments, that can be used in any combination. The Committee noted these treatments included levodopa therapies, non-ergot dopamine agonists, monoamine-oxidase-B inhibitors, catechol-O-methyltransferase inhibitors, and amantadine.

Health need

7.11. The Committee considered that the health need for people with Parkinson's disease is high due to the progressive nature of the disease with motor and psychological symptoms that are eventually debilitating. The Committee considered that the unmet health need to be addressed by this application was unclear, given the application proposed a listing of rotigotine without eligibility restrictions. The Committee considered that the burden of Parkinson's disease was severe and the evidence for this was moderate strength and quality.

7.12. The Committee considered that the reported incidence of Parkinson's disease in Māori and Pacific peoples was lower compared to non-Māori, non-Pacific peoples (Pitcher et al. 2018). The Committee considered this difference may, in part, reflect inequities in access to diagnostic specialist services for Māori and Pacific peoples. The Committee noted the reported incidence was not considered up to date however, it was considered that this was the most recently available data.

7.13. The Committee noted that two Parkinson's disease scales were commonly used in clinical trials, the Hoehn and Yahr scale and the Unified Parkinson's Disease Rating Scale (UPDRS).

- The Committee noted that the Hoehn and Yahr scale tracks progression of Parkinson's disease over time over five stages of dysfunction, with a median transit time of 20-62 months depending on the stage. The Committee noted that the minimally clinical meaningful difference (MCID), and therefore the measured efficacy of different treatments, varies by each stage of the Hoehn and Yahr scale. The Committee considered this was a complicated area of research given the significant variability within the scale. The Committee noted that the application under consideration would encompass the treatment of disease at all of the stages of the Hoehn and Yahr scale.

- The Committee noted that in contrast to the Hoehn and Yahr scale measuring motor symptoms, the UPDRS encompasses both motor and non-motor symptoms, doing so in in four domains (non-motor, motor in daily living, motor examination, and motor complications). The Committee noted that the UPDRS is updated on a two-to-four-year cycle and that study results using different versions of the scale may not be comparable. The Committee noted that trials may be powered for different parts of the UPDRS and therefore report different clinical endpoints. The Committee noted that the UPDRS allowed for individuals to move up and down the scale according to their clinical condition. The Committee considered that the reported MCID in the UPDRS was not consistent throughout the research literature, but considered this to fall between a 3-to-5-point reduction on the UPDRS in the motor subsection(s).

- The Committee considered that the Hoehn and Yahr scale is comparable to the motor score of the UPDRS, and the full UPDRS score also considers health-related quality of life for the person.

Health benefit

7.14. The Committee considered that treatment of early Parkinson's disease is focussed on treating motor symptoms and limiting impact of the disease on a person's daily life. The Committee considered that treatment of advanced Parkinson's disease is focussed on limiting off time and augmentation, among other clinical features.

7.15. The Committee noted its previous considerations of the following direct randomised, placebo-controlled trials or indirect comparisons of trials:

- SP513 trial (Giladi et al. Mov Disord 2007;22: 2398-404)
- SP515 (CLEOPATRA-PD) trial (Poewe et al. Lancet Neurol 2007;6:513-20)
- RECOVER trial (Trenkwalder et al. Mov Disord. 2011;26:90-9)
- Network meta-analysis indirectly comparing trials: Thorlund et al. Neuropsychiatr Dis Treat. 2014;10:767-76

7.16. The Committee further considered the following evidence when assessing this application:

- Sanford & Scott. CNS Drugs. 2011;25:699-719
  A narrative systemic review up to July 2011 of the use of transdermal rotigotine in Parkinson's disease patients up to 37 weeks. Six studies were included across early and advanced Parkinson's disease. In early Parkinson's disease, rotigotine initiated without levodopa had reportedly significantly greater improvements than placebo in the UPDRS. In advanced Parkinson's disease, rotigotine in combination with levodopa reportedly reduced 'off' time and improved motor functioning and ADL significantly more than levodopa plus placebo. Rotigotine did not meet a prespecified response-rate noninferiority criterion compared to ropinirole, although the authors noted the doses used may not have been directly comparable. Rotigotine was reportedly non-

inferior to oral pramipexole in reducing 'off' time, although it did not meet a response-rate noninferiority criterion (SP515 trial). Rotigotine was reported to improve morning motor functioning and reduced sleep disturbances, night-time motor symptoms, depressive symptoms, pain and functioning, and quality of life to a significantly greater extent than placebo. Rotigotine was stated to be generally well tolerated across the trials and in longer-term extension studies.

- Rizos et al. Eur J Neurol. 2016;23(8):1255-61
  A retrospective and prospective observational survey using medical records and clinical interviews of 425 people with Parkinson's disease. Participants were either already taking dopamine agonists including ropinirole extended release, pramipexole extended release and rotigotine transdermal patches, or were initiated on a dopamine agonist during the study. Participants were matched according to on sex, age, documented Parkinson's disease diagnosis and duration of disease, age at Parkinson's disease onset, past use of dopamine agonists (dose and duration), discontinuation of past dopamine agonists and reason for discontinuation, duration of current dopamine agonist use, use of any other antiparkinsonian medication, and comorbid conditions. People with clinically judged dementia were not included. Findings suggested a relatively low incidence of emergent impulse control disorders (ICD) associated with long acting or transdermal dopamine agonists. ICD rates with rotigotine patch (4.9%) as well as with pramipexole-prolonged release (6.6%) were significantly less than for other dopamine agonist formulations (pramipexole IR (19.0%; $P< 0.05$)). 50.9% of Parkinson's disease patients presenting with ICD needed to discontinue dopamine agonist therapy. Confounders or potential information bias not assessed included levodopa induced dyskinesias, possible effect of previous therapies on observed ICD, and the use of validated tools for ICD diagnosis (used interview of clinical staff).

- Garcia-Ruiz et al. J Neurol Neurosurg Psychiatry. 2014;85:841-5
  A multicentre transversal (observational cross-sectional) of ICD prevalence in people with Parkinson's disease chronically treated (>6 months) with a single non-ergot dopamine agonist (pramipexole, ropinirole, or rotigotine). 39% had ICD (n=91), the non-ICD group comprising the residual 61% (n= 142). It was reported that the main differences between the ICD and non-ICD groups were type of dopamine agonist intake and age. Oral dopamine agonist treatment (pramipexole and ropinirole) was associated with higher risk of ICD compared with transdermal dopamine agonist (rotigotine); of people treated with oral dopamine agonists, 84/197 (42%) developed ICD compared to 7/36 (19%) of those treated with transdermal dopamine agonists (Fisher's exact text <0.01). The authors concluded that as pramipexole, ropinirole and rotigotine are all non-ergot dopamine agonists with very similar pharmacodynamic profiles, it is likely that other factors, including route of administration (transdermal vs oral), explain the difference in risks of ICD development.

- Chen et al. J Pharm Pharm Sci. 2017;20:285-94
  A meta-analysis with systemic literature searches of Cochrane library, PubMed and Embase databases up to April 2016 for randomised controlled trials in early to advanced Parkinson's disease comparing rotigotine against placebo, measuring any combination of the following UPDRS Part III and Part II scores, 'off' time, adverse events, serious adverse events, or discontinuation because of adverse events as outcomes. Pooling of the studies suggested that for patients with early or advanced PD, rotigotine could significantly improve UPDRS Part III and Part II scores *(*$P< 0.001$) but had significantly higher incidence of adverse events than the placebo ($P< 0.001$). The authors concluded that rotigotine can improve daily living and motor ability of patients with PD, although it has higher reported incidence of adverse events.

- Chen et al. Eur J Neurol. 2022; 30:762-73
  A network meta-analysis comparing indirectly the efficacy, tolerability and safety of six commonly used non-ergot dopamine agonists in advanced Parkinson's disease. A total of 34 RCTs (7868 patients) were included in the study. Analysis suggested six

commonly used non-ergot dopamine agonists are effective as an adjunct to levodopa in advanced Parkinson's disease. Ropinirole prolonged-release was associated with the best improvement in UPDRS-II, UPDRS-III, and UPDRS-II + III (0.811, 0.742, and 0.827). For off-time reduction, pramipexole immediate release ranked first (0.979), and ropinirole prolonged release ranked first in off-time responder rate (0.927). Pramipexole extended release ranked first in overall withdrawals, and rotigotine transdermal patch ranked first in the incidence of adverse events (≥1 AEs).

7.17. The Committee noted the following evidence included in the application:

- Pagonabarraga et al. Parkinsons Dis. 2015; 2015:131508,1-7
- Kim JM et al. BMC Neurol. 2015;15:17
- Kesayan et al. Degener Neurol Neuromuscul Dis. 2015;5:63-72
- Raeder et al. CNS Drugs. 2021;35:215-31

7.18. The Committee considered that rotigotine was non-inferior to other non-ergot dopamine agonists in the treatment of early or advanced Parkinson's disease.

7.19. The Committee considered that there did not appear to be an evidence-based treatment paradigm available for Parkinson's disease, and the typical sequencing of treatments was not clear from the literature. The Committee considered that choice of pharmacotherapies would be dependent on the assessment and preferences of the individual clinician. The Committee considered that agents from different classes are often used together to limit the need for higher doses of any one agent, thus minimise the side effects and maximise effect. The Committee considered that the primary benefit of funding rotigotine patches as an additional treatment option would be increased prescriber choice with therapeutic flexibility.

7.20. The Committee considered that primary literature for rotigotine use in Parkinson's disease was abundant. The Committee considered the randomised control trial evidence used instrumental estimates of efficacy with only a limited number of study results reaching the threshold of MCID. The Committee considered that this placed the efficacy of rotigotine at the margin of clinical meaningfulness in the context of Parkinson's disease.

7.21. The Committee noted that there are randomised control trials published that consider sub-groups within the Parkinson's disease indication, including efficacy in different ethnic groups and sub-indications such as sleep disturbance or other non-motor symptoms, however, evidence to support additional benefit in these groups was not considered by the Committee.

7.22. The Committee considered the evidence that rotigotine is associated with a reduction in the risk of ICD was based on spontaneous reports and post-marketing epidemiological prevalence surveys and noted an estimate that to prevent one event of ICD, 1,000 people would need to be treated with rotigotine. The Committee considered that this adverse event was rare but severe. The Committee considered that the reduction in ICD risk associated with rotigotine could be due to a lessened efficacy of rotigotine compared to other dopamine agonists.

7.23. The Committee considered that the research literature for Parkinson's disease treatment was complex, needing specialist interpretation as to the appropriate treatment paradigm and utility of rotigotine for Parkinson's disease. The Committee also considered that further advice could be sought from the Neurological Advisory Committee regarding the estimated size for Parkinson's disease subgroups that could be considered to have a different health need and potential different benefit from rotigotine patches, for example,

people with impulse control disorders or psychiatric disorders requiring dopamine agonist treatment.

7.24. The Committee considered that further advice could be sought from the Neurological Advisory Committee about use of rotigotine for people who are unable to take oral tablets in hospital, for example, those who are a surgical admission or those with vomiting or diarrhoea, to prevent withdrawal symptoms, due to their different acute health need and suitability considerations when compared to crushed or opened tablets or capsules.

7.25. The Committee considered other psychological manifestations from dopaminergic treatment include hallucinations, sleep disturbance and depression and anxiety. The Committee considered that the incidence of psychosis in those treated with non-ergot dopamine agonists could be as high as 14%. The Committee noted that this was treated with dopamine antagonists (clozapine) on an individual basis under specialist supervision.

7.26. The Committee considered that a significant focus of the research literature was on the on-off time related benefit from treatment with non-ergot dopamine agonists. The Committee considered that for ergot dopamine agonists (cabergoline) heart valve adverse events are well estimated, however this is not well modelled for the non-ergot dopamine agonists.

7.27. The Committee considered that adverse effects associated with rotigotine treatment would be similar to other non-ergot dopamine agonists, with an additional consideration of skin reactions from patch application. The Committee considered that the rate of adverse events was reported as higher in those using rotigotine (Chen et al. 2022).

7.28. The Committee noted that rotigotine patches are funded in Australia. The Committee considered that anecdotally, the dose of rotigotine is more difficult to control due to the long-acting nature of the transdermal formulation and noted anecdotal information that in circumstances where termination of rotigotine is required the withdrawal period is longer than for other non-ergot dopamine agonists. The Committee understood that generally use in Australia has varied by prescriber preference and experience in prescribing rotigotine patches for Parkinson's disease.

7.29. The Committee considered that the evidence for the health benefit from rotigotine for family whānau was not clear.

7.30. The Committee considered there was no evidence for significant health system consequences should rotigotine be funded.

7.31. The Committee considered that off-label prescribing of rotigotine patches was unlikely outside of the Parkinson's disease or restless legs syndrome indications.

Suitability

7.32. The Committee considered that the current funded treatment options for people who are unable to take oral medications, short-term or otherwise, include crushed or opened tablets or capsules or infusions of apo-morphine. The Committee considered that some tablet or capsule formulations, including modified or extended-release forms, are not easily crushed or administered via nasogastric tube.

7.33. The Committee considered that there was some weak evidence including case studies, retrospective cohort studies and narrative reviews to support the use of rotigotine in people unable to take solid oral dosage forms. The Committee considered that the use of transdermal rotigotine in the acute setting was under specialist consensus.

7.34. The Committee considered a scoping review on pill burden in those with advanced Parkinson's disease that reported use of rotigotine patches for those without safe oral

access is widely recommended throughout narratives and anecdotal clinical cases (Kim et al. J Palliat Med. 2023:26:131-41)

7.35. The Committee noted a survey of 71 people with Parkinson's disease in New Zealand that reported that people taking treatment experience pill burden as an issue. It was noted that the authors recommended education and support rather than a switch from an oral formulation to a transdermal formulation (Oad et al. Dysphagia. 2019;34:119-28).

7.36. The Committee considered that for a person with a complex treatment regimen, with multiple dose times, and multiple agents, the reduction of one oral agent would reduce pill burden but that the impact of that on a person's quality of life was unclear. The Committee considered the evidence for reduction in pill burden in those with Parkinson's disease to be weak.

7.37. The Committee considered that the formulation of rotigotine patches has a significant effect on the absorption and pharmacokinetic release profile. The Committee noted that skin thickness also could impact absorption and use in those with thinner skin, as in older people typically, could have more rapid absorption. The Committee considered the re-formulation of patches would impact this release profile.

Cost and savings

7.38. The Committee considered that it was difficult to identify the specific currently funded comparators for rotigotine because there was no clear hierarchy, sequencing or algorithm for pharmacotherapies for the treatment of Parkinson's disease. The Committee considered that people would currently be receiving a range of treatment regimens, as different treatments were tried in various combinations and dosages to maximise therapeutic efficacy while minimising the risk of adverse events.

7.39. The Committee considered that if rotigotine was funded for Parkinson's disease, that use of rotigotine may partially replace use of current funded non-ergot dopamine agonists, such as ropinirole and pramipexole. The Committee considered that rotigotine and other non-ergot dopamine agonists would be used in combination with other classes of medicines.

7.40. The Committee noted that in Australia and England, rotigotine comprised a relatively small portion of the market for dopamine agonists. The Committee considered that, if rotigotine was funded for Parkinson's disease, usage patterns in New Zealand were likely to be similar to patterns observed in other countries.

Summary for assessment

7.41. The Committee considered that the PICO (population, intervention, comparator, outcomes) for rotigotine if it were to be funded in New Zealand for Parkinson's disease was unclear due to a lack of a well-defined target population, uncertainty regarding where rotigotine would sit within the treatment paradigm, and the lack of a clear set of comparators. (When sufficient information is available, a PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. A PICO may develop based on new information, additional clinical advice, or further analysis by Pharmac staff.)

7.42. The Committee considered that the PICO could be developed based on advice to be sought from the Neurological Advisory Committee.

Population	Parkinson's disease [Not able to be further defined at this stage]
Intervention	Rotigotine patches
Comparator(s)	[Not able to be defined at this stage]
Outcome(s)	[Not defined at this stage]
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

8. Rotigotine for Restless legs syndrome

Application

8.1. The Committee reviewed an application for rotigotine for the treatment of restless legs syndrome.

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

Recommendation

8.3. The Committee **recommended** that rotigotine for restless legs syndrome be listed as **cost neutral** to currently funded non-ergot dopamine agonists, such as pramipexole or ropinirole.

8.4. The Committee considered that the clinical and suitability benefit above other currently funded non-ergot dopamine agonists or gabapentinoids was not clear for those with restless legs syndrome in making this recommendation.

Discussion

Māori impact

8.5. The Committee discussed the impact of funding rotigotine for the treatment of restless legs syndrome (RLS) on Māori health areas of focus and Māori health outcomes. The Committee considered that there was a lack of evidence of the prevalence of RLS in Māori compared to people of other ethnicities in New Zealand. The Committee acknowledged that Māori are inequitably burdened by comorbidities that may increase the risk of RLS such as diabetes, renal failure, hypertension, and cardiovascular disease.

Health need

8.6. The Committee noted that restless legs syndrome is characterised by irresistible urge to move the limbs to alleviate a sensation of dysesthesia or hyperesthesia, with symptoms worsening at rest and night-time. The Committee noted main consequence of this is sleep disturbance with individuals with restless legs syndrome are two to three times more likely to report difficulty initiating and maintaining sleep, and non-restorative sleep as well as depressive or anxiety disorders.

8.7. The Committee noted that the pathophysiology of RLS is unknown. The Committee noted that people with end stage renal disease, cardiovascular disease, iron deficiency and pregnant people are at an elevated risk of developing RLS (Ohayon et al. 2012; Vlasie et al. 2022). The Committee considered that most cases of RLS are idiopathic in cause, progressive in nature or with a familial component.

8.8. The Committee noted that RLS affects between up to 14% of the population (Ohayon et al. 2012). The Committee considered that this prevalence was a potential overestimation

due to the impact and variability of physician judgement in diagnosis and treatment of RLS. The Committee considered that the reported prevalence rates of RLS among the epidemiological literature were highly variable and the evidence was generally of low quality. The Committee considered that those who want pharmacological treatment for RLS it was possible that this comprised a very large group of people.

8.9. The Committee considered that there was a lack of evidence around the prevalence of RLS in Māori or Pacific peoples compared to people of other ethnicities in New Zealand. The Committee acknowledged that Māori and Pacific peoples are inequitably burdened by comorbidities that increase the risk of RLS such as diabetes, renal failure, hypertension, and cardiovascular disease.

8.10. The Committee considered that the current diagnostic criteria for RLS were relatively broad. The Committee noted that the severity scale for RLS was a points system which assessed the disruption to a person's life associated with RLS. The Committee noted that the severe RLS was defined as experiencing symptoms more than 16 times per month.

8.11. The Committee considered that diagnosis of RLS was likely occurring in primary care rather than by neurologists or other specialists.

Health benefit

8.12. The Committee considered that Pharmac staff could seek further advice regarding the use of rotigotine from GPs as they are the practitioner most likely to be involved in the diagnosis of RLS and prescribing of treatment.

8.13. The Committee noted that rotigotine is a non-ergot dopamine agonist delivered via a transdermal patch system. The Committee noted that rotigotine has previously been considered by PTAC for Parkinson's disease but not RLS.

8.14. The Committee considered that the treatment paradigm for RLS begins with lifestyle interventions such as sleep hygiene, with use of pharmacotherapies reserved for those with severe symptoms. The Committee considered that funded options for pharmacotherapy include gabapentin, pregabalin as first line options and non-ergot dopamine agonists or levodopa agents as second line treatments. The Committee considered that if funded, rotigotine would likely be a second line treatment option in addition to the currently available non-ergot dopamine agonists (ropinirole or pramipexole).

8.15. The Committee considered that non-ergot dopamine agonists or levodopa agents are typically used second line due to concerns about augmentation and an increased risk of worsening movement disorders with use of dopaminergic treatments compared to gabapentinoids. The Committee considered that, in general, there was a focus on treatment of refractory symptoms and reduction of augmentation.

8.16. The Committee noted that the clinical instrument for RLS is the International Restless Legs Syndrome Scale (IRLSS) with a minimally clinically important difference of -5 on the motor subsection(s).

8.17. The Committee considered the following evidence for this application:

- Trenkwalder et al. Lancet Neurol. 2008;7:595-604
  A randomised, double-blind, placebo-controlled trial with 458 people with moderate to severe idiopathic restless leg syndrome diagnosed based on the four cardinal features of the International Restless Legs Syndrome Study Group (IRLSSG), with either previous positive dopamine agonist treatment or no previous treatment. Participants were randomised to either 1 mg (n=148), 2 mg (n=96), 3 mg (n=92) or placebo (n=114). Mean treatment difference in IRLS sum score compared to placebo at the end of the maintenance phase as follows (p<0·0001): –5·3 (95% CI, –7·6 to –

2·9) in those who actually received 1 mg, –7.7 (95% CI, –10·3 to –5·0) in those who actually received 2 mg group, and –8.0 (95% CI, –10·7 to –5·4) in those who actually received 3 mg group. Treatment difference in CGI item 1 score was also recorded. Skin reactions, mostly mild or moderate, were seen in 43% of those who received rotigotine and 2% of those who received placebo, none of which required hospitalisation. Ten patients had a serious adverse event that was related to rotigotine. The rate of typical dopaminergic side-effects in patients who received rotigotine was low; no signs of augmentation were noted.

- Garcia-Borreguero et al. Eur J Neurol. 2012;19:1385-96
  A review of the scientific literature up to 31 December 2011 for the drug classes and interventions employed in RLS treatment. Previous guidelines were accessed. Five studies were considered within the guidelines and the assessment of evidence for the treatment of restless legs syndrome including non-ergot dopamine agonists. Rotigotine patches (1-3 mg/24 h) were considered effective for short and long-term treatment of primary RLS while ropinirole (2-3 mg daily) and pramipexole (0.25-0.75 mg daily) were considered effective for short-term treatment and possibly effective for long-term treatment. In particular, a 5-year prospective study reported that the overall 5-year incidence of clinically significant augmentation was 13.2%. Augmentation was dose dependent, 5.1% of patients experienced this at 1–3 mg/24 h, whilst 8.1% were receiving 4 mg/24 h. Rotigotine (and other funded non-ergot dopamine agonists) was considered effective and recommended for short- and long-term use for RLS.

- Winkelmann et al. Mov Disord. 2018;33:1077-91
  An evidence-based review aiming to evaluate the therapeutic interventions for RLS. The authors concluded that transdermal rotigotine is efficacious at doses of 2-3 mg (previously considered likely efficacious). It was reported that there is insufficient evidence for the 1 mg dose of rotigotine, and 0.5 mg dose of rotigotine is not efficacious. Long-term trials with rotigotine need to be undertaken to monitor local site reactions and augmentation, and dose and treatment duration dependence need to be taken into consideration. Further study is needed exploring the biological mechanism of augmentation and possible methods to reduce the risk and severity of its occurrence. Other agents assessed included gabapentinoids, opioids, iron, bupropion, clonidine, vitamin C and E and non-pharmacological interventions.

8.18. The Committee also noted the following evidence in this application:

- Oertel et al. Sleep Med. 2010; 11:848-56
- Inoue Y et al. Sleep Med. 2013; 14:1085-91
- Iftikhar et al. Eur J Neurol. 2017; 24:1446-56

8.19. The Committee considered that any advantages of rotigotine compared to other non-ergot dopamine agonists were unclear and considered that rotigotine could provide an additional option within the non-ergot dopamine agonist class.

8.20. The Committee considered that from the application submitted there do not appear to be specific clinical settings, or sub-groups of people with RLS, where rotigotine would be the preferred pharmacotherapy option.

Suitability

8.21. The Committee noted all other funded treatment options for RLS are oral tablet or capsule formulations. The Committee considered the patch formulation of rotigotine offered a suitability benefit when considering those unable to take oral medications.

8.22. The Committee considered that the benefit of a patch formulation was not clear in the context of treating RLS. The Committee considered that this would likely be a very small group of people with RLS.

Cost and savings

8.23. The Committee noted that the number of individuals with RLS in New Zealand has likely increased over time due to changes to diagnostic criteria. The Committee considered that between 10% and 80% of cases may receive treatment but that a range of non-pharmaceutical and pharmaceutical treatment options would likely be tried before a clinician considered treatment with rotigotine should it be funded.

8.24. The Committee considered that if rotigotine was listed without restrictions, use would predominantly occur among people with Parkinson's disease and RLS. The Committee noted that rotigotine would be considered an additional option for treatment for people with risk factors for levodopa-related complications, people with contraindications to gabapentinoids, and people for whom oral medications are unsuitable or a patch is considered a preferable treatment option.

Summary for assessment

8.25. The Committee considered that the PICO (population, intervention, comparator, outcomes) for rotigotine if it were to be funded in New Zealand for RLS was unclear due to a lack of a well-defined target population and the lack of a clear set of comparators. (When sufficient information is available, a PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. A PICO may be developed based on new information, additional clinical advice, or further analysis by Pharmac staff.)

8.26. The Committee considered that the PICO could be developed based on advice to be sought from primary care advisors.

Population	Restless legs syndrome [patient population able to be further defined at this stage]
Intervention	Rotigotine patches
Comparator(s)	[Not able to be defined at this stage]
Outcome(s)	[Not defined at this stage]
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

9. Ketamine for community use in individuals receiving palliative care with intractable pain not adequately controlled with opioids

Application

9.1. The Committee reviewed the application for ketamine for community use in individuals receiving palliative care with intractable pain not adequately controlled with opioids.

9.2. The Committee noted that, at its August 2022 meeting, PTAC requested this application be brought to the Committee for a full review of available evidence, following review of the meeting record from the August 2022 Analgesic Specialist Advisory Committee.

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

Recommendation

9.4. The Committee **recommended** that ketamine injection 100 mg per ml (2 ml vial) for community use in individuals receiving palliative care with intractable pain not adequately

controlled with opioids be listed in Section B of the Pharmaceutical Schedule with a **low priority**.

> **KETAMINE** – Subsidy by endorsement
> Subsidised only if endorsed, for use for a patient receiving palliative care who has intractable pain that is not managed adequately with current therapy for end-of-life care.

9.5. In making this recommendation, the Committee considered:

- The high health need of those with intractable pain receiving palliative care in a community setting, such as those in hospice or home-based care;
- The health need of the whānau caring for a person receiving palliative care experiencing intractable pain unresponsive to opioids;
- The paucity of published evidence of benefit, and the published evidence of potential harm (Hardy et al J Clin Oncol. 2012;30:3611-7), balanced alongside the considerable clinical experience, of palliative medicine specialists and hospital-based acute pain services, that ketamine may provide a health benefit for those receiving palliative care with intractable pain;
- The potential cost-savings to the health system, of funding ketamine in the community setting for this group of people;
- The potential to reduce the number of people requiring hospital admission for management of intractable pain in palliative care;
- That it is important to ensure equitable access to treatment for those for whom hospital admission for administration of ketamine would not be practical;
- That funding ketamine in the community setting for this group of individuals could provide more equitable palliative care treatment, as it would allow individuals to be treated in hospice and/or in their homes in their last days.

9.6. The Committee considered that due to the considerable safety considerations associated with ketamine use and administration, it should only be used for individuals receiving palliative care with intractable pain not adequately managed with other end-of-life treatments.

Discussion

Māori impact

9.7. The Committee discussed the impact of funding ketamine for palliative care in the community setting on Māori health areas of focus and Māori health outcomes. The Committee considered that funding ketamine in this setting may be beneficial for Māori, who may prefer to receive palliative care at home, supported by their whānau rather than in a hospital setting.

Background

9.8. The Committee noted that the use of ketamine in the palliative care setting has been discussed extensively since 2009, with the Analgesic Specialist Advisory Committee most recently recommending it for funding in the community palliative care setting with a high priority (May 2022). The Committee noted that it reviewed the records from the Analgesic Specialist Advisory Committee meeting in May 2022, and recommended that the item come back to PTAC to review the evidence in full.

9.9. The Committee noted that in 2012 it considered the evidence for ketamine burst therapy in the published paper by Hardy et al. (J Clin Oncol. 2012;30:3611-7), which reported no

evidence of benefit for ketamine over placebo in pain management in patients with intractable pain unresponsive to opioids (record unpublished). The Committee also noted that Pharmac had and has received a number of Named Patient Pharmaceutical Assessment applications for the use of ketamine in the palliative setting, all of which were for continuous ketamine therapy, as opposed to burst therapy, and for when spinal anaesthesia was unsuitable or impractical.

Health need

9.10. The Committee considered that the health needs of individuals receiving palliative care with intractable cancer pain have been well described previously, most recently in the record of the Analgesics Specialist Advisory Committee's May 2022 meeting. The Committee noted that the primary purpose of palliative care is to improve the quality of life of individuals towards the end of their life, and potentially also helping to support their family and whānau during this time.

9.11. The Committee noted that ketamine, in various presentations, is currently funded in Section H of the Pharmaceutical Schedule without restriction. The Committee noted that ketamine is not listed in Section B of the Pharmaceutical Schedule and is therefore not funded for use in the community setting, which precludes access to those receiving hospice or home-based palliative care. The Committee considered that there consequently is a high health need for those receiving palliative care in the community with intractable pain that cannot be effectively managed with other treatments. People in this setting would need to be admitted to hospital to access ketamine infusions, which could be a barrier for some, especially people living rurally, those without transport options or for those who would prefer to receive treatment at home.

Health benefit

9.12. The Committee noted that the use of ketamine in the palliative care setting is primarily driven by protocol and the recommendations by speciality palliative medicine/care groups, and that there is limited clinical evidence for the use of ketamine therapy in end-of-life care, despite there being evidence in treatment settings outside of palliative care for its use in seizure control and analgesia. The Committee noted that guidelines for the use of ketamine in palliative care state that it should only be initiated by a specialist, and occasionally by a general practitioner whilst the individual receiving care remains under the care of a palliative medicine specialist who can advise on appropriate dosing.

9.13. The Committee noted that adverse effects of ketamine treatment include upper gastrointestinal, hepatobiliary, urinary, and neuropsychiatric toxicity.

9.14. The Committee noted the following evidence relating to the use of ketamine in palliative care:

- Hardy et al. J Clin Oncol. 2012;30:3611-7: a dose-escalation, double-blind, randomised, placebo-controlled trial in which subcutaneous ketamine was administered as 3 to 5 day burst therapy in the management of cancer pain. The intention-to-treat sample comprised 185 patients (ketamine, 93; placebo, 92). Of these, 149 met the definition of completion. Seventy-four participants received study drug on all 5 days. The number of patients needed to treat for one additional patient to have a positive outcome from ketamine was 25 (95% CI, six to ∞). The number needed to harm, because of toxicity-related withdrawal, was six (95% CI, four to 13). The authors concluded that ketamine does not have net clinical benefit when used as an adjunct to opioids and standard co-analgesics in the treatment of cancer pain.

- Marchetti et al. Eur J Pain. 2015;19:984-93: a 5-year retrospective cohort study involving testing ketamine by intravenous in-hospital administration, then a conversion to an oral route, or oral treatment directly administered at home. Among 55 cases (51 patients, neuropathic pain 60%), the mean effective oral dose was 2 mg/kg. Ketamine

was effective in 24 patients (44%, mean pain reduction 67 ± 17%), partially effective in 20% (mean pain reduction 30 ± 11%).

- Pickering et al. Anesthesiology. 2020;133:154-64: a randomised, double-blind, crossover, placebo-controlled study in 20 patients with refractory neuropathic pain who were ketamine-naïve. Patients received one infusion every 35 days in a random order: ketamine (0.5 mg/kg)/placebo or ketamine (0.5 mg/kg)/magnesium sulphate (3 g) or placebo/placebo. The primary endpoint was the area under the curve of daily pain intensity for a period of 35 days after infusion, which was not significantly different between the three groups (N = 20) over 35 days (mean area under the curve = 185 ± 100, 196 ± 92, and 187 ± 90 pain score-days for ketamine, ketamine/magnesium, and placebo, respectively, P = 0.296)

- Salas et al. J Palliat Med. 2012;15:287-93: a randomised, double-blind, placebo-controlled trial designed to assess efficacy of continuous intravenous infusion of ketamine in patients suffering from cancer pain refractory to opiates who had been admitted to palliative care units. Secondary objectives were to assess patients' satisfaction with and tolerance of ketamine. Twenty patients were analysed (11 received ketamine and 9 received placebo). Self-reported pain did not differ between the two groups, as the symptoms continued to evolve during the study period. The tolerance for ketamine was reported as satisfactory.

- Jonkman et al. Curr Opin Support Palliat Care. 2017;11:88-92: a review of the benefit of ketamine in the treatment of terminal cancer pain that is refractory to opioid treatment and/or complicated by neuropathy. Authors reported that while randomised controlled trials consistently show lack of clinical efficacy of ketamine in treating cancer pain, a large number of open-label studies and case series show benefit.

- Goldman et al. J Palliat Med. 2019;22:1154-61: a review examining the efficacy of ketamine for the treatment of depression and physical pain in palliative care patients. Ketamine's effect on treating physical pain was mixed with the largest and most recent randomised controlled trials suggesting no significant analgesic effect.

- Benini et al. Drugs Context. 2021;10:2021-2-5: a review analysing the use of ketamine in children and the potential extension of its applications in paediatric palliative care (PPC). The authors reported that the use of ketamine in PPC should be more widely considered due to its overall favourable safety profile and efficacy, which are supported by an increasing number of studies, although in settings different from PPC and of mixed quality.

9.15. The Committee considered that, overall, the strength and quality of evidence was weak. The Committee considered that there is evidence of poor effectiveness for the use of ketamine in this setting, and that the studies were very heterogeneous (palliative care versus chronic pain, varying pain types, ketamine was occasionally supplemental to other therapies, variable duration of treatment and of treatment benefit, variable dose and administration route) and that the studies had relatively few participants or were uncontrolled non-comparative individual case reports. The Committee also noted that there are also often various other conditions that may also be present when an individual has a terminal illness, such as anxiety and depression. The Committee noted that adverse events commonly reported associated with ketamine were somnolescence (sleepiness), psychotomimetic symptoms, and cystitis.

9.16. The Committee also noted a review examining the efficacy of ketamine for the treatment of depression and physical pain in palliative care patients (Goldman et al. J Palliat Med. 2019;22:1154-61). The Committee noted that the evidence for the efficacy of ketamine in treating physical pain was mixed, and all studies included in the Goldman et al. review reported antidepressant effects of ketamine in this population. The Committee considered the quality-of-life gain from mood improvements during end-of-life care to be

beneficial but noted that there currently is no evidence to support a benefit with longer-term ketamine treatment.

9.17. The Committee considered it unlikely that better quality data would be forthcoming in this space, as palliative care physicians are already widely using ketamine in palliative care, and it is difficult to conduct randomised trials with individuals who are receiving end-of-life care.

9.18. The Committee also considered that individuals who respond favourably to ketamine while in hospital may benefit from ongoing therapy outside of hospital (ie via hospice or home-based palliative care) for a short duration of time.

9.19. The Committee noted that ketamine has an effect characterised by a steep concentration-response curve, with high variability between individuals. The Committee noted that treatment with ketamine can quickly escalate from analgesia to anaesthesia. The Committee considered that it was important to not cause distress to individuals, or their family/whānau, at end of life, and that risk mitigation with regard to adverse events and diversion would need to be carefully considered if ketamine were to be funded in the community setting.

9.20. The Committee considered that, on balance, the potential health benefits of ketamine for intractable pain in people receiving palliative care who have no funded alternatives outweigh the potential for adverse effects from treatment with ketamine. The Committee also considered that ketamine treatment would be ceased quickly if the individual receiving treatment did not receive obvious clinical benefits.

Suitability

9.21. The Committee considered that if ketamine were funded in community for use in palliative care it would be administered via an infusion, and that this would need to be supported by health care professionals as those receiving treatment or their whānau or caregivers would not be able to administer the medication. The Committee considered that people receiving palliative care in the community were most likely to already be receiving support from health care professionals regarding the administration of their other medications (eg opioid infusions/subcutaneous injections) and care.

9.22. The Committee noted that the following formulations of ketamine are listed in Section H of the Pharmaceutical Schedule: 1 mg per ml for injection (100 ml bag), 10 mg per ml for injection (10 ml syringe), and 100 mg per ml (2 ml vial). Members considered that the 100 mg per ml (2 ml vial) presentation would be most appropriate for use in the community as this would allow administration via a syringe driver at various concentrations.

Cost and savings

9.23. The Committee noted that the estimated number of individuals receiving ketamine in the palliative care setting ranges widely and that the estimates by Pharmac staff were reasonable. The Committee noted that the number of people who may be eligible could therefore be as low as 75 per annum and as high as 600-700 annually. The Committee considered that ketamine being offered in the palliative care setting in the community may reduce the burden on hospital inpatient resources, as these individuals would not then require admission to hospital for the management of their pain.

9.24. The Committee considered that any interventions, pharmacological or related to health care resource, used to manage any adverse effects of ketamine would likely be minimal given the treatment would be used in the end-of-life care setting.

Summary for assessment

9.25. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ketamine if it were to be funded in New Zealand for the management of intractable pain in palliative care in the community. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals receiving palliative care in the community who have intractable pain not adequately controlled with usual analgesia (including strong opioids)
Intervention	**Ketamine burst therapy** (approximately 80% of the treatment group) Treatment duration of 3-5 days. Initial dose of 50 or 100 mg/24 hr (starting dose of 25 mg in some more frail patients), if pain persists and no unacceptable adverse effects are experienced, escalate to 300 mg/24 hr, and finally to a maximum dose of 500 mg/24 hr. **Ketamine continuous infusion** (approximately 20% of the treatment group) 1 to 2.5 mg/kg per 24 hours for a maximum of 1 week. Used in conjunction with opioids and potentially other adjuncts.
Comparator(s)	Best supportive care, which may include opioid analgesic escalation/rotation (methadone included), antineuropathic analgesics, regional analgesia where available, and lidocaine infusion
Outcome(s)	Improved management of pain and health-related quality of life
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

10. Darolutamide and non-metastatic castration resistant prostate cancer

Application

10.1. The Committee reviewed the application for darolutamide in the treatment of high risk non-metastatic castration resistant prostate cancer (nmCRPC).

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

Recommendation

10.3. The Committee **recommended** that darolutamide be listed with a **high priority**.

Initial application – (non-metastatic castration resistant prostate cancer) any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Patient has prostate cancer; and
2. Patient does not have distant metastasis
3. Patient's disease is castration resistant; and
4. Patient has a PSA doubling time of 10 months or less during continuous ADT; and
6. Patient has not had prior subsidised treatment with darolutamide.

Renewal – (high-risk non-metastatic castration resistant prostate cancer) only from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Clinically stable disease; and/or
2. No distant metastasis

10.4. In making this recommendation the Committee considered:

- The high-quality randomised control trial evidence for a health benefit, with moderate strength evidence on overall survival, with data up to three years in comparison to placebo;

- That darolutamide provides comparable clinical efficacy to apalutamide, which received a high priority recommendation from CTAC in April 2022;

- That Māori and Pacific peoples experience inequitable outcomes from prostate cancer generally, however access to darolutamide specifically is considered unlikely to reduce these more systemic inequities.

Discussion

Māori impact

10.5. The Committee noted that Māori and Pacific peoples experience inequitable outcomes from prostate cancer, as they are more likely to present with advanced disease, and consequently have a higher mortality rate than non-Māori and non-Pacific peoples. The Committee considered that the higher likelihood of diagnosis in later disease stages may be due to lower rates of opportunistic prostate specific antigen (PSA) screening in these populations. The Committee noted that for this reason, Māori are less likely to be treated while their disease is still non-metastatic, and therefore less likely to have nmCRPC.

10.6. The Committee considered a study undertaken in the Northern region of New Zealand that reported Māori men were less likely to have had opportunistic PSA screening tests undertaken compared to non-Māori men (25.4% vs 46.1% of the total aged-matched region population; $P < 0.001$). The authors concluded that the difference in the rates of opportunistic screening tests by ethnicity had influenced the incidence and clinical significance of the cancers diagnosed (Matti et al. BJU Int. 2020;128(S3):11-17). Cancers detected in Māori men were 73% more likely to be of high grade (Gleason 8 or above), compared to those in non-Māori men (Matti et al, 2020). Therefore, the Committee considered, while Māori may be less likely to be part of the nmCRPC subgroup overall, they may be more likely to have high risk disease if they are in the nmCRPC group.

10.7. As the current treatments for nmCRPC are less efficacious than for those with non-metastatic prostate cancer that is not castrate resistant, the funding of darolutamide may provide this population with improved quality of life and an increase in the time to disease progression.

Background

10.8. The Committee noted that it had previously reviewed an application for apalutamide, in February 2020 and September 2020, where PTAC deferred making a recommendation pending additional information and advice from the Cancer Treatments Subcommittee of PTAC (CaTSoP; now the Cancer Treatments Advisory Committee - CTAC), as well as in February 2021 where PTAC gave no formal recommendation. In April 2022 CTAC recommended apalutamide with a high priority as it considered there was high quality randomised controlled trial evidence for a health benefit from apalutamide in terms of overall survival and metastasis free survival (MFS). CTAC also considered quality of life was improved with apalutamide maintenance treatment likely due to increased MFS. The PTAC noted apalutamide has a similar mechanism of action to darolutamide, for the same indication.

10.9. The Committee noted that the population eligible for treatment with darolutamide would be the same as that considered for apalutamide, which represents a subset of those with prostate cancer.

Health need

10.10. The Committee considered that the intent of treatment is to defer progression to more symptomatic disease and metastatic disease, in order to maintain quality of life for people with nmCRPC. The Committee considered people with nmCRPC are asymptomatic, with a good quality of life for their age, despite expected side effects from androgen-deprivation therapy (ADT) or complications from surgical or radiation treatment (eg urinary incontinence, bowel symptoms or erectile dysfunction). However, they would be likely to develop metastases, particularly if considered high risk by PSA doubling time.

10.11. The Committee considered that most individuals with nmCRPC were prescribed continued ADT with a gonadotrophin-releasing hormone (GnRH) agonist and monitored through "watch and wait" for disease progression, despite the fact that by definition, those with CR PC were no longer sensitive to ADT. The current funded agents for ADT are goserelin, bicalutamide and flutamide.

10.12. The Committee noted that they had previously noted that acquired F876L androgen receptor mutation in advanced prostate cancer cells confers resistance to enzalutamide, and may also confer resistance to apalutamide, but that it appears darolutamide may not be similarly affected by the F876L mutation or other known androgen receptor (AR) mutations (PTAC, February 2020). The Committee considered whether there was any effect of the F876L androgen receptor mutation on the efficacy of treatment in those with nmCRPC. The Committee noted that less than 2% of the population with nmCRPC prior to radiation therapy had the mutation. The Committee considered that there was no clinical trial data on the effect of the mutation before or after treatment, and that this did not impact the benefit for most.

Health benefit

10.13. The Committee noted that darolutamide is an androgen receptor (AR) inhibitor with a flexible polar-substituted pyrazole structure that binds with high affinity directly to the receptor ligand binding domain. Darolutamide competitively inhibits androgen binding, AR nuclear translocation, and AR mediated transcription. Darolutamide treatment decreases prostate tumour cell proliferation leading to potent antitumour activity.

10.14. The Committee noted that darolutamide does not cross the blood brain barrier, and has minimal binding to GABA receptors, resulting in less central nervous system side effects, in comparison to apalutamide. The Committee noted that darolutamide and other therapeutics of the same class are usually administered in combination with ADT, which itself can reduce quality of life due to side effects (eg urinary incontinence, bowel symptoms or erectile dysfunction).

10.15. The Committee considered the Fizazi et al. NEJM. 2019;380:1235-46 study, a pivotal phase 3 randomised (2:1) clinical trial (ARAMIS). The trial investigated metastasis-free survival (MFS) as the primary endpoint, in 1509 adults with nmCRPC treated with either darolutamide (+ADT) or placebo (+ADT). The Committee noted that this trial reported a MFS of 40.4 months vs 18.4 months in the darolutamide-treated arm compared to placebo-treated (hazard ratio [HR] for metastasis or death in the darolutamide group, 0.41; 95% confidence interval (CI), 0.34 to 0.50; P<0.001).

10.16. The Committee also considered Fizazi et al. NEJM. 2020;383:1040-9, the open-label extension follow up of ARAMIS after unblinding following primary MFS analysis, which reported an overall survival (OS) at 3 years of 83% for darolutamide (+ADT) (95% CI, 80% to 86%) vs 77% for the placebo (+ADT) arm (95% CI, 72% to 81%).

10.17. The Committee noted an indirect comparison of side effects in trials with people with nmCRPC when administered apalutamide (SPARTAN trial, as Smith et al, N Engl J Med 2018; 378:1408-18), enzalutamide (PROSPER, as Sternberg et al, N Engl J Med 2020; 382:2197-206), or darolutamide (ARAMIS), published in 2021. The Committee considered the baseline characteristics of the participants in the ARAMIS trial to be similar to the SPARTAN trial. The Committee noted this study reported that, compared

with apalutamide and enzalutamide, darolutamide was associated with statistically significantly lower absolute risks for falls, fractures, and rash. In comparison to enzalutamide, darolutamide was also associated with a statistically significantly lower absolute risk of mental impairment disorder, fatigue not including asthenia and severe fatigue not including asthenia (Halabi et al. J Urol. 2021; 206:298-307).

10.18. There was no significant difference in discontinuation rates due to adverse events between darolutamide and placebo in the ARAMIS trial (8.9% darolutamide vs 8.7% placebo) (Fizazi et al, 2020). The Committee also noted that proportionately more participants in the treatment arm of the SPARTAN trial discontinued in comparison to the treatment arm of the ARAMIS trial (14.9 vs 7.3% apalutamide treatment vs placebo in SPARTAN, and the above 8.9% vs 8.7% darolutamide treatment vs placebo in ARAMIS). The Committee considered that the evidence available indicates that darolutamide may be better tolerated in comparison to apalutamide. The Committee considered that treatment should aim to improve health-related quality of life, as well as delay progression to metastatic disease, and that avoiding adverse events that may lead to less discontinuation.

10.19. The Committee noted that the placebo group had an increased survival time in the SPARTAN trial in comparison to the placebo group in the ARAMIS trial (18.4 vs 16.1 months, respectively). The Committee noted that comparison of the trials' outcomes after metastasis, like OS, may be limited due to the difference in subsequent treatments available in the SPARTAN and ARAMIS trials. The Committee noted that crossover in the trials had been noted previously as a possible driver of differences between trial outcomes, although the Committee considered subsequent treatment to be the more significant source of bias in comparisons of longer-term outcomes between SPARTAN and ARAMIS.

10.20. Members noted the first subsequent anti-cancer treatments in the ARAMIS trial were abiraterone 13%, docetaxel 49%, enzalutamide 18% and other 13% in the treatment group, whilst in the placebo group they were abiraterone 23%, docetaxel 66%, enzalutamide 19% and other 16% (Fizazi et al. 2019). In the SPARTAN trial the first subsequent anti-cancer treatment was abiraterone 76%, docetaxel 9%, enzalutamide 12%, and other 3% in the treatment group, whilst in the placebo group it was abiraterone 74%, docetaxel 8%, enzalutamide 13% and other 5%(Smith et al. 2018).

10.21. The Committee also considered the crossover data in ARAMIS from those who crossed over from placebo to darolutamide following unblinding. Approximately 31% of those who received placebo received darolutamide. The Committee considered three models of analysis that adjusted for crossover for OS, that reported similar results of a HR of 0.66-0.69. The Committee noted that the results suggest crossover did not substantially overstate OS in the comparator arm of ARAMIS (Shore et al. JCO, 2021;39(6) Suppl.:240-240).

10.22. The Committee noted an anchored matching-adjusted indirect comparison (MAIC) using patient-level data.

10.23. The Committee further noted other published indirect comparisons of darolutamide, enzalutamide and apalutamide including:

- Chowdhury et al. Adv Ther. 2022; 39:518-53
- Kumar et al. Urol Oncol, 2020;38:826-34
- Mori et al, Int J Clin Oncol. 2020;25:1892-1900
- Mulati et al. Front Oncol, 2021;11:733202
- Roumiguie et al. Future Oncol. 2021;17:1811-23.

10.24. The Committee noted that Chowdhury et al. 2022 reported significant differences in MFS times (apalutamide + ADT vs darolutamide + ADT [98.3%; HR 0.70 (95% CrI 0.51, 0.98)], however no difference in OS between darolutamide and apalutamide was observed. The Committee considered interpretation of these results was limited by it being a supplier-sponsored MAIC study that only indirectly compared treatments, using patient-level data that matched a non-randomised post-hoc defined subset of patients in the SPARTAN trial against patients in the ARAMIS study.

10.25. The Committee also noted evidence regarding sequencing of abiraterone followed by enzalutamide. The Committee noted advice from CTAC (April 2022) that abiraterone should not be used in those people with nmCRPC previously treated with apalutamide. PTAC also noted the use of abiraterone following a second-generation anti-androgen is funded in other countries. The Committee further noted sequencing of abiraterone followed by enzalutamide was reported to have a longer time to PSA progression compared to the reverse sequence, however no difference in OS was noted (Cattrini et al, Cancers (Basel). 2021;13:4522, Tran et al, CADTH Health Technology Review; 2021). The Committee considered that in metastatic disease clinical practice in New Zealand is starting to favour docetaxel over abiraterone. The Committee noted that the treatment regime in the ARAMIS trial, and associated apparent increases in OS, is applicable to New Zealand with regards to the subsequent use of docetaxel occurring in 49% of those treated with darolutamide after progression (Fizazi et al. 2019). The Committee noted that approximately 13% of those in the darolutamide treated group in ARAMIS received abiraterone as the first subsequent anticancer therapy (Fizazi et al. 2019).

10.26. The Committee considered that, given the similar health benefit of darolutamide compared with other agents in this class, a competitive process that could result in the funding of a single agent from this class would be reasonable.

Suitability

10.27. The Committee noted that the oral formulation of darolutamide offered a similar benefit to those with nmCRPC as apalutamide. This would be administered in combination with ADT, which is a subcutaneous injection every 12 weeks.

Cost and savings

10.28. The Committee noted that the number of people in this group was previously estimated by CTAC to be approximately 10 patients per year in Auckland, but that patient numbers are uncertain, and Pharmac estimates since have been higher to account for a prevalent surge of patients. The Committee noted the current Pharmac estimate of 90-120 for New Zealand over the first five years and considered that this may be reasonable in current practice, to reflect a prevalent group of people who have been diagnosed with nmCRPC experiencing reasonably good survival, and some people with metastatic disease being diagnosed as non-metastatic using current methods.

10.29. The Committee noted that people with nmCRPC are identified as not having distant metastasis by means of conventional radiological imaging, however, clinical practice is moving rapidly to prostate-specific membrane antigen positron emission tomography (PSMA PET) scanning as the preferred imaging technique to exclude the presence of distant metastases in prostate cancer diagnosis and work-up. The Committee noted that whilst this is not applicable necessarily to all hospitals or locations within New Zealand currently, a study of 200 people with suspected nmCRPC reported approximately 55% had evidence of distant metastatic disease when scanned using PSMA PET (Fendler et al, Clin Cancer Res. 2019;25:7448-54). The Committee considered it likely that the population with nmCRPC may be reduced in the future, since more people who would currently be considered to have non-metastatic disease would be found to have metastatic prostate cancer at diagnosis.

10.30. The Committee noted the lower rate of discontinuation in clinical studies of those treated with darolutamide vs placebo in comparison to apalutamide vs placebo ((Fizazi et al, 2020; Smith et al. 2018). The Committee considered that this was probably due to fewer side-effects with darolutamide.

Summary for assessment

10.31. The Committee considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for darolutamide if it were to be funded in New Zealand for nmCRPC. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with castration-resistant prostate cancer with no distant metastasis and who are at a high risk of developing distant metastases as defined by a PSA doubling time of ≤10 months (HR nmCRPC).
Intervention	Darolutamide (oral tablets) + androgen deprivation therapy (ADT) - The recommended dose of apalutamide is 600mg (two 300mg tablets) administered twice-daily. - Treatment ongoing until evidence of metastatic disease. - Goserelin
Comparator(s) (NZ context)	ADT only (goserelin (1x10.8mg subcutaneous injection every 12 weeks and bicalutamide 50 mg tab once daily)
Outcome(s)	• Improved MFS, with median OS of 40.4 months with darolutamide vs 18.4 months with placebo (hazard ratio 0.41, 95% CI 0.34-0.50) • Improved OS, with 3-year survival of 83% with darolutamide vs 77% with placebo (hazard ratio 0.69, 95% CI 0.53-0.88) • Improved time to pain progression (hazard ratio 0.65, 95% CI 0.53-0.79) • Improved time to first use of cytotoxic chemotherapy (hazard ratio 0.58, 95% CI 0.44-0.76)
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

11. Methylnaltrexone bromide for the treatment of opioid induced constipation outside of palliative care

Application

11.1. The Committee reviewed the application for methylnaltrexone bromide subcutaneous injection for the treatment of opioid induced constipation outside of palliative care.

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

Recommendation

11.3. The Committee **recommended** that methylnaltrexone bromide for opioid induced constipation outside of palliative care be funded in Section H of the Pharmaceutical Schedule with a low priority.

Initiation — (Opioid induced constipation outside of palliative care)
All of the following:

1. Individual has opioid induced constipation; and
2. Oral and rectal treatments for opioid induced constipation, including bowel-cleansing preparations, are ineffective or inappropriate; and
3. Mechanical bowel obstruction has been excluded; and
4. Treatment is for a maximum of 14 days duration.

- In making this recommendation, the Committee considered:

11.3.1 The high health need of individuals with opioid induced constipation for whom other laxatives are not effective or are inappropriate;

11.3.2 That the likely benefit would be for those people who are in hospital with refractory opioid induced constipation for whom mechanical bowel obstruction has been excluded (and where availability in Schedule H of the Pharmaceutical Schedule would allow funded access to Te Whatu Ora public hospital inpatients only in this (non-palliative care) setting).

11.4. The Committee recommended that methylnaltrexone bromide for opioid induced constipation outside of palliative care not be funded in Section B of the Pharmaceutical schedule for use in the community setting.

11.5. The Committee considered that there were no issues with the suitability of methylnaltrexone bromide in this setting.

Discussion

Māori impact

11.6. The Committee discussed the impact of funding methylnaltrexone bromide for the treatment of opioid induced constipation on Māori health areas of focus and Māori health outcomes. The Committee noted that there is limited data available relating to rates of opioid induced constipation amongst the Māori population compared to other ethnicities and considered that the impact of funding methylnaltrexone for this indication on Māori health outcomes is unknown at this time.

Background

11.7. The Committee noted that methylnaltrexone bromide subcutaneous injection is currently funded under Special Authority for the treatment of opioid induced constipation in individuals receiving palliative care. The Committee noted that it reviewed an application in May 2019 to widen access to methylnaltrexone bromide to those with opioid induced constipation outside of palliative care. At that time, the Committee recommended funding this with a low priority, and suggested the application be reviewed by the Analgesic and Gastrointestinal Subcommittees of PTAC (now the Analgesic Advisory and Gastrointestinal Advisory Committees respectively) regarding appropriate eligibility criteria due to the potentially large population which may be prescribed methylnaltrexone bromide.

11.8. The Committee noted that the application was reviewed by the Analgesic Advisory Committee in May 2022, where methylnaltrexone bromide was recommended for funding with medium priority. The Committee also noted that at this meeting, the Analgesic Advisory Committee had estimated that approximately 1600 people may receive this treatment annually, which was significantly higher than numbers previously estimated. The Analgesic Advisory Committee had also considered that the highest health need was in people with chronic non-cancer pain with opioid induced constipation, as these individuals would likely be taking opioids for extended periods of time. Following its review of this record, at its meeting in August 2022, PTAC Members requested that the funding application for methylnaltrexone bromide be brought back to PTAC for review.

11.9. The Committee noted that the Gastrointestinal Advisory Committee (August 2022) had also reviewed the May 2022 Analgesic Specialist Advisory Committee's record for methylnaltrexone bromide. The Gastrointestinal Advisory Committee had considered that, although gastroenterologists typically do not treat this cohort of individuals, methylnaltrexone bromide could be used in a potentially large group of individuals who are prescribed opioids in the post-operative setting.

Health need

11.10. The Committee noted that methylnaltrexone was currently funded already on the Pharmaceutical Schedule in Section B under Special Authority criteria for people in the community receiving palliative care for, in effect, those whose constipation is refractory or intolerant to oral and rectal treatments for opioid induced constipation.

11.11. The Committee noted that, according to a report by the Health Quality and Safety Commission New Zealand, in 2019, an average of 16.6 per 1,000 people in Aotearoa New Zealand received a strong opioid, and that 'weak' opioids are prescribed at a rate of 98.8 per 1,000 people, and that this prescription rate increased with age. The Committee noted that there is no available data on the rates of opioid induced constipation in New Zealand, nor is there a breakdown of opioid induced constipation for any subgroup. The Committee also considered that it would be inappropriate to extrapolate this from the palliative care setting.

11.12. The Committee considered that the health need of people in hospital with opioid induced constipation was higher than that of people in the community setting (aside from those in the community receiving end-of-life care under the care of palliative care services).

11.13. The Committee considered that people in the community with opioid induced constipation have a large number of funded alternatives, and that the contributing factors to constipation for individuals in the community may be modifiable with medication and lifestyle changes.

- The Committee noted that other factors may exacerbate constipation in people who are taking opioids and are hospitalised. These include the use of general or spinal anaesthesia, the need for a high level of opioids following surgery, suppressed motility with bowel stasis in response to abdominal surgery, and reduced ambulation. In addition, the Committee noted that in the hospital setting there are some types of surgery, for example obstetrics or gynaecological surgery, whereby opioid induced constipation can be difficult to treat, and often needs to be avoided to minimise any damage to the anatomical area where the surgery has occurred.

- The Committee considered that there are a number of available funded laxatives in the hospital setting and that for the majority of those affected these are appropriate. Members considered that a common contributing factor to constipation in hospital is a lack of physical mobility when individuals are on longer periods of bed rest, confounded by age and fragility. The Committee also noted that for some individuals three days without laxation could still be their normal bowel habit. The Committee considered that it was therefore important that any eligibility criteria for methylnaltrexone bromide be targeted to ensure access be only for those individuals for whom other laxatives have been ineffective or inappropriate.

- . The Committee considered that mechanical bowel obstruction is a common cause of apparent 'constipation' (absent bowel motions, sometimes with overflow diarrhoea) that remains unresponsive to laxatives in the hospital setting, and that is was important to rule out obstruction as a cause before treatment with methylnaltrexone bromide.

- Members considered that currently, manual disimpaction for individuals with opioid induced constipation is rarely undertaken on medical or surgical wards, and that those

in hospital will likely receive sequential bowel cleansing preparations (eg Glycoprep/Kleanprep or Prepkit). Members considered that contrast media (eg Gastrografin) is also usually given to confirm/rule out mechanical bowel obstruction and that can also have a therapeutic effect.

Health benefit

11.14. The Committee noted that methylnaltrexone bromide is not Mesdafe approved for opioid induced constipation outside of palliative care.

11.15. The Committee noted that the use of methylnaltrexone bromide in those who have not experienced a bowel movement following other treatments for constipation poses a risk to the individual if a bowel obstruction has not been ruled out. The Committee noted that administering methylnaltrexone bromide to these individuals may cause bowel perforation.

11.16. The Committee noted that recently there has been an increase in co-prescribing of laxatives with opioids following surgery, and considered that, if access to methylnaltrexone bromide was widened, it may become an early-line option due to its ease of administration.

11.17. The Committee noted the following evidence regarding the use of methylnaltrexone bromide for opioid induced constipation:

- Mehta et al. F1000res. 2021;10:891: a post-hoc analysis of two randomised trials in adults with chronic non-cancer pain for at least two months and opioid induced constipation for at least 30 days treated with methylnaltrexone bromide or placebo once daily for four weeks. The study reported that the proportion of patients who experienced rescue-free bowel movement within four hours after the first dose of study treatment ('responders') was greater among all patients who received methylnaltrexone bromide (25.1%, n=226/900) compared with placebo (8.8%, n=32/363; *P*<0.0001) and that more individuals treated with subcutaneous versus oral methylnaltrexone bromide were responders (34.2%, n=102/298 and 20.6%, n=124/602, respectively).

- Brenner et al. Support Care Cancer. 2021;9:5209-18: a post-hoc analysis of three randomised trials in individuals with cancer and opioid induced constipation treated either with methylnaltrexone bromide or placebo. The study reported that after 24 hours, the proportion of patients achieving a response was the same as at 4 hours for the methylnaltrexone bromide-treated group (70.4%) but increased to 50.0% of patients who received placebo (*P*=0.1555).

- Candy et al. Cochrane Database Syst Rev. 2022;9:CD006332: an assessment of the effectiveness and safety of mu-opioid antagonists (MOAs; included naldemedine, naloxone, and subcutaneous methylnaltrexone bromide) for opioid-induced bowel dysfunction in people with cancer and people at a palliative stage irrespective of the type of terminal disease. Subcutaneous methylnaltrexone bromide versus placebo was reported to have a risk of spontaneous laxations within 24 hours with fourfold greater than placebo (risk ratio (RR) 2.97, 95% CI 2.13 to 4.13. 2 trials, 287 participants,). Risk of spontaneous laxations in the medium term was over tenfold greater with methylnaltrexone bromide (RR 8.15, 95% CI 4.76 to 13.95, 2 trials, 305 participants, I^2 = 47%. NNTB 2, 95% CI% 2 to 2%; moderate-certainty evidence).

11.18. The Committee considered that the evidence noted above supported the use of methylnaltrexone bromide for short term use only, and that a duration of use of up to 2 weeks would be sufficient for anyone hospitalised. The Committee considered that any individuals with opioid induced constipation that continues beyond 2 weeks should have a treatment plan aimed at reducing the requirement for opioids.

11.19. The Committee considered that the evidence for use of methylnaltrexone bromide to produce laxation was of a high-strength and quality compared to placebo but noted that there was minimal evidence comparing methylnaltrexone bromide to other laxatives. The Committee also considered that there was strong biological plausibility for the use of methylnaltrexone bromide in this setting.

Suitability

11.20. The Committee considered that methylnaltrexone bromide is easily administered in the hospital setting.

Cost and savings

11.21. The Committee considered that the number of individuals who may be treated with methylnaltrexone bromide, outside palliative care settings, for opioid-induced constipation was highly uncertain and there was a high risk of use of methylnaltrexone bromide outside the intended target population. The Committee considered that if methylnaltrexone bromide was funded in the community setting that there would be a high fiscal risk,

11.22. The Committee noted that post-operative constipation prolongs the length of time that some individuals may stay in hospital and considered that the use of methylnaltrexone bromide in the hospital oncology setting may reduce the mean length of time that people with oncological conditions stay in hospital. The Committee noted that this could result in some savings to the health sector due to lower utilisation of hospital resources, but the magnitude of these savings was uncertain. The Committee noted that many people with general surgical conditions, and other individuals with opioid-induced constipation, would not be discharged from hospital until they have had a bowel motion. The Committee considered that this treatment may reduce the length of hospital stay for anyone in hospital with opioid-induced constipation.

Funding criteria

11.23. The Committee considered that methylnaltrexone bromide would be best placed following other funded laxatives agents (including bowel cleansing preparations) in the paradigm of treatment of non-palliative opioid induced constipation.

11.24. Members also considered that it was important to rule out mechanical obstruction before treating anyone with methylnaltrexone bromide, to mitigate the risk of bowel perforation, and that this should be included as in the eligibility criteria for funded access. The Committee considered that contrast media would be used to rule out mechanical bowel obstruction, and that this may have the desired laxation effect alongside its use as a diagnostic.

11.25. The Committee also considered that methylnaltrexone bromide would be most appropriate as a short-term treatment for opioid induced constipation, and that individuals on longer-term opiate treatment for chronic non-cancer pain with constipation should be managed by other means (such as a reduction in opiate treatment).

Summary for assessment

11.26. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for methylnaltrexone bromide if it were to be funded in New Zealand for treatment of opioid induced constipation outside of palliative care. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People in hospital with intractable opioid-induced constipation, outside of palliative care, for whom oral and rectal treatments are ineffective or unable to be tolerated.
Intervention	12 mg subcutaneous injection of methylnaltrexone bromide every alternate day
Comparator(s)	Bowel prep and/or gastrografin, rarely manual disimpaction may be considered
Outcome(s)	Reduced time to bowel movement. • Methylnaltrexone bromide treatment was associated with increased rescue-free bowel movement within four hours after the first dose compared to placebo (RR 3.74, 95% CI = 3.02-4.62) (Zhang et al. Pain Ther. 2021;10: 165-179)
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	