Record of the Analgesics Advisory Committee Meeting held on 5 May 2022

Analgesics Advisory Committee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) Specialist Advisory Committees 2021.

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

The Analgesics Advisory Committee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

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

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1. Attendance

Present

Giles Newton-Howes (Chair)
Tipu Amir
Leinani Aiono-Le Tagaloa
Brian Anderson
Catherine D'Souza
Bruce King
Jane Thomas
Alana Wilson
Howard Wilson

Apologies

Christopher Lynch

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Ketamine (community use)	High Priority
• Lidocaine hydrochloride 10% subcutaneous (SC) infusion	High Priority
• Levetiracetam (subcutaneous)	Medium Priority
• Methylnaltrexone bromide subcutaneous injection	Medium Priority

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Analgesics Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-Committee-Terms-of-Reference.pdfThe Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

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

3.3. The Analgesics Advisory Committee is a Specialist Advisory Committee of Pharmac. The Analgesics Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Analgesics Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Analgesics that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Analgesics that differ from the Analgesics Advisory Committee's, or Specialist

Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

3.4. Pharmac considers the recommendations provided by both the Analgesics Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for Analgesics.

4. Welcome and introduction

4.1. The chair welcomed the meeting attendees and noted the commitment of the various discussion leads, and also noted the resignation from the committee of Dr Howard Wilson and his meritorious service.

5. Record of Analgesics Subcommittee meeting held Tuesday, December 3, 2019

5.1. The Committee noted and accepted the record of the previous meeting held on 3 December 2019.

6. Previous recommendations made

6.1. The Committee noted their previous recommendation that lidocaine (lignocaine) gel 2%, urethral syringe be widened to include the treatment of intractable rectal pain/tenesmus and noted that lidocaine (lignocaine) gel 2%, urethral syringe has been open listed since September 2020.

6.2. The Committee noted their previous recommendation that the application for doxylamine for the treatment of nausea or vomiting of pregnancy be declined and noted that since that recommendation, the application has undergone public consultation and been declined.

6.3. The Committee noted that they recommended Pharmac seek the advice of the Cancer Therapeutics Advisory Committee (CTAC, formerly CaTSoP) on the increased use of aprepitant for nausea and vomiting. Pharmac staff intend to seek advice around use of aprepitant from CTAC at a later date.

6.4. The Committee considered that the request to review opioid usage trends can be considered a standing item on the agenda for all future Analgesic Advisory Committee meetings.

7. Correspondence and Matters Arising

Paracetamol 1000 mg/ibuprofen (as sodium dihydrate) 300 mg in 100 ml solution for infusion for acute pain (Maxigesic IV)

7.1. The Committee noted and agreed with the PTAC recommendation to decline the funding application for paracetamol 1000 mg/ibuprofen (as sodium dihydrate) 300 mg in 100 ml solution for infusion for acute pain (Maxigesic IV) and had no additional comments.

Buprenorphine depot injections

7.2. The Committee noted and agreed with the Mental Health Advisory Committee recommendation to fund buprenorphine depot injection (Buvidal weekly and Buvidal

monthly) for the maintenance treatment of patients with opioid use disorder dependence and buprenorphine depot injection (Sublocade) for the treatment of opioid use disorder, noting that PTAC had reviewed the Mental Health Advisory Committee records and recommended that the Analgesic Advisory Committee be asked for their advice, given opioid dependence and addiction may coexist in patients with chronic non-cancer pain.

7.3. The Committee note that they have no additional comments.

8. Therapeutic Group and NPPA Review

Expenditure Summary

8.1. The Committee noted the summary of community expenditure on pharmaceuticals in the anaesthetics, analgesics and antinausea and vertigo agents therapeutic sub-groups

8.2. The Committee considered expenditure on paracetamol to have increased drastically over the past financial year and noted that increased use due to COVID-19 was unlikely to be the sole explanation to account for the difference in expenditure, but likely to be the most significant factor driving utilisation. Pharmac staff noted that as the prices of products fall progressively through repeated competitive procurement, competition tends to decline, and prices become closer to the marginal cost of production. Pharmac staff noted that both factors mean that the price of an older product can be expected to rise again after a number of years of sustained low prices and explain the increased costs of paracetamol.

8.3. The Committee have recommended Pharmac staff provide further detail to the Committee about the use and cost of paracetamol, specifically by geographical location, and ethnicity to enable a more nuanced comment at later meetings.

8.4. The Committee noted an increase in the use of oxycodone.

8.5. The Committee recommended Pharmac consider an overview of all Practitioners supply order (PSO) drugs. Should Pharmac consider the Committee's input would be useful, then a list of all anaesthetics, analgesics and antinausea and vertigo agents on the current PSO list would need to be reviewed as an initial step. The Committee considered a parallel process would be potentially useful for all relevant therapeutic groups to undertake should a broader review of the PSO list occur. The Committee recommended this as a likely beneficial action by Pharmac.

Funding applications progressing towards decline

8.6. The Committee noted that Pharmac has been progressing a project to assess 'inactive' funding applications for decline. 'Inactive' in this context refers to the fact that Pharmac has not been actively undertaking any work to progress the applications for funding. The Committee noted that Pharmac has publicly consulted on a number of funding applications over the last 3 years and are supportive of this work.

8.7. The Committee noted the application for buprenorphine patches required additional information to enable progression. Members of the Committee supported not moving the application towards a decline as there may be a clinical role for atypical opioids such as buprenorphine in the management of chronic pain. However, the Committee would need to see a future application with updated evidence of efficacy and safety in this setting to provide formal advice. The Committee noted the anecdotal benefit of atypical opioid use in Australia as opposed to prescription of strong opioids such as oxycodone for management of chronic non-cancer pain.

8.8. The Committee noted that the funding application for capsaicin 0.075% cream for cannabinoid hyperemesis syndrome was bought to PTAC following public consultation that included additional information from the applicant. PTAC recommended the application progress towards a decline.

Named Patient Pharmaceutical Assessment (NPPA)

8.9. The Committee considered NPPA applications received since 1 December 2019 for pharmaceuticals in the anaesthetics, analgesics and antinausea and vertigo agents therapeutic subheadings.

8.10. The Committee noted a number of NPPA applications had been received for cannabidiol and other cannabis-based products. The Committee noted that an application for the listing of cannabidiol with tetrahydrocannabinol (Sativex) had previously been assessed by PTAC in August 2015 and had been recommended for decline. The Committee noted that no other funding application has been received by Pharmac for the funding of any other cannabidiol or cannabinoid product.

8.11. The Committee noted that the use of cannabis and related products in the management of pain (among a variety of conditions) is a growing field of research and of considerable clinical interest. The Committee consider it likely there will be future applications received by Pharmac and increasing NPPA applications. The Committee noted that the current state of evidence is insufficient to consider this part of routine clinical practice and the role of cannabinoids in the analgesics area remains unclear.

8.12. The Committee noted a number of applications had been received and approved for ketamine for use in the palliative care setting. The Committee noted that ketamine is a last-line treatment in palliative care and noted there is an application to be reviewed in the context of the current meeting.

8.13. The Committee noted that there have been NPPA applications for oxcarbazepine for trigeminal neuralgia. Pharmac staff note that there is an application for oxcarbazepine for second-line epilepsy treatment that has received clinical advice and has been ranked on the Options for Investment list. The Committee consider that oxcarbazepine should be considered for broader indications than epilepsy, including trigeminal neuralgia due to a better adverse effect profile in patients who do not tolerate carbamazepine.

Anaesthetics

Lidocaine 2% gel, urethral syringe

8.14. The Committee noted the increased usage of lidocaine 2% gel, urethral syringe and consider that the suitability of a syringe versus a gel tube may contribute to the high usage. The Committee noted there could be other reasons for the increased usage that they are unaware of.

Lidocaine cream 4%

8.15. The Committee noted that lidocaine cream 4% use has declined over time and consider that this could be due to movement across to using the lidocaine 2% gel tube. The Committee noted that continuity of supply may not be important and that Pharmac staff could seek further advice regarding the consideration of delisting lidocaine cream 4%.

Lidocaine cream 2.5% with prilocaine 2.5%

8.16. The Committee noted that there has been an increase in the use of lidocaine with prilocaine and noted this could be due to the increase in COVID-19 vaccinations in the last year.

Analgesics

8.17. The Committee noted an application for morphine sulphate 5 mg/ml pre-filled syringes for acute pain. The Committee noted that there are currently four presentations of morphine sulphate pre-filled syringes on the HML and considered there was no unmet need in acute pain that wasn't sufficiently met with the currently funded products.

8.18. The Committee noted that, as a general rule, it would be beneficial to understand analgesic use across different indications, such as acute pain, chronic non-cancer pain and cancer pain. The rationale for this was to provide clearer advise as to the utilisation of various analgesics in context

Opioid analgesics

8.19. The Committee noted that there is an upcoming supply issue for morphine hydrochloride oral liquid. The Committee considered the oral formulations of morphine hydrochloride were essential across a number of clinical indications and noted that palliative care and paediatrics could be disproportionally affected by any supply issues. The Committee noted that there is a need for both low and high strength doses of oral morphine hydrochloride and that the palatability of the product for patients is an important consideration for any oral formulation. The Committee recommended Pharmac staff consult widely across the sector about any changes in the supply of oral morphine hydrochloride.

8.20. The Committee noted that when looking at the unadjusted data for opioid use there was variation across ethnicities. The committee noted that the data itself did not enable a more detailed review of this. Factors such as differences in population age structures between different ethnic populations (where there would need to be a large discrepancy in patient numbers to observe a significant difference), differences in underlying disease prevalence and access to treatment may account for some of these differences. The Committee expressed the view that more detailed analysis may help identify some of these issues.

8.21. The Committee noted that there appeared to be differences between DHBs regarding opioid dispensing across New Zealand and considered this was a serious issue. This included codeine, fentanyl, oxycodone, and tramadol. The Committee recommended Pharmac consider how to address this across the health sector and considered that it is important there is adequate education around the use of opioid analgesics and the relative risks and benefits of their use in different clinical settings.

8.22. The Committee considered what actions Pharmac may usefully engage in to ensure appropriate monitoring of opioid usage, and actions to minimise the risk of an opioid epidemic, as has occurred overseas in the US, Canada, and Australia. The Committee recommended that Pharmac provide regional opioid use data to all DHBs in order to enable them to investigate these patterns of use locally. The Committee recommended work be undertaken to develop national benchmarking to enable ongoing monitoring at the DHB level.

8.23. The Committee considered that Pharmac could engage with other stakeholders in the health sector who share an interest in this area. This could include the Health Quality and Safety Commission NZ (HQSC) and the Ministry of Health. Such

collaborations would strengthen monitoring and subsequent appropriate action minimise the risk of patient and wider societal harm.

Buprenorphine transdermal patches

8.24. The Committee noted an application for buprenorphine transdermal patches for severe chronic non-cancer pain that had received a recommendation for decline from PTAC in May 2019, based on insufficient evidence of long-term analgesic benefit, lack of evidence regarding functional improvements and improvements in health-related quality of life, and concerns regarding diversion and possible societal harm.

8.25. The Committee noted recent correspondence regarding this application received in response to recent public consultation on the decision to decline a number of funding applications. The applicant suggested that the original application was considered through a lens of conventional opioid analgesics, and that ANZCA/FPM and New Zealand Society of Anaesthetists groups have recommended use of atypical opioids before typical opioids in the setting of chronic non-cancer pain.

8.26. The Committee considered they had no additional comments and support PTAC's recommendation for decline, however the Committee agreed to review further updated evidence if presented in the future.

Fentanyl patches in chronic non-cancer pain

8.27. The Committee noted that fentanyl patches have been listed with no restriction for fully funded access since 2015 and concerns have been raised about the possibility of inappropriate/unsafe prescribing of fentanyl patches in the setting of chronic non-cancer pain. The Committee considered that education around the use of fentanyl patches in this setting has not been successful to date. Pharmac staff note that placing a funding constraint may not manage access, as prescribing can still occur and would potentially negatively impact equity of access for patients benefiting from these medicines in the cancer pain setting. The Committee recommended fentanyl be particularly considered in any ongoing work to further monitor opioid prescribing due to its high potency.

Non-opioid analgesics (excluding NSAIDs)

8.28. The Committee noted there has been an increase in the use of celecoxib. The Committee considered that celecoxib is commonly used over ibuprofen as the favoured NSAID and there is increased use in primary care practice.

Antinausea and vertigo agents

8.29. The Committee noted that discontinuation of prochlorperazine tab 3 mg buccal would unlikely have a major impact due to other currently listed formulations but acknowledged that there may be specific patient groups for whom it would fulfil an important aspect of usability.

Other therapeutic groups of relevance

8.30. The Committee noted that buprenorphine with naloxone (suboxone) is currently restricted to patients who are opioid dependent and engaged with an opioid treatment service approved by the Ministry of Health (MoH).

8.31. The Committee considered a request to revisit prescriber type, noting that currently only those working at an approved opioid treatment service can apply for the Special

Authority. The Committee considered the current prescriber type was appropriate, noting the potential risk of increased inappropriate use if widened.

Horizon scanning

8.32. The Committee noted that tapentadol hydrochloride is an opioid-like drug used to treat moderate to severe acute pain. The Committee noted that the supplier previously withdrew an application to register tapentadol with Medsafe in New Zealand. The Committee noted that Medsafe has not received a new application seeking registration of this medicine, and Pharmac has not received a funding application for tapentadol.

9. Ketamine (community use) - Pain - palliative care patients with intractable pain not adequately controlled with opioids [P-001040]

Application

9.1. The Committee considered ketamine for community use in palliative care patients with intractable pain not adequately controlled with opioids.

9.2. The Committee noted that Pharmac staff sought advice from palliative care specialists in late 2021 to help inform the assessment of ketamine for this indication.

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 be listed in Section B of the Pharmaceutical Schedule for the treatment of palliative care patients in the community with intractable pain not adequately controlled with opioids with a **high priority** within the context of analgesic, anti-emetic and anaesthetic treatments, subject to the following endorsement:

> KETAMINE – Subsidy by endorsement
> Subsidised only if endorsed by a palliative care specialist, relevant specialist, or relevant practitioner on the recommendation of a palliative care specialist or relevant specialist, for a patient 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 needs of palliative care patients with intractable pain not adequately controlled with opioids and the impact on their family/whānau who experience substantial distress due to this.

- Noted that there are inherent challenges in undertaking research in a palliative care setting, and as such, that the evidence base for pain management in palliative care is presently limited in terms of strength and quality.

- Considered that the low-quality evidence that does exist suggests that ketamine improves pain control for some palliative care patients with intractable pain not adequately controlled with opioids and that it has a manageable adverse effect profile in the context of end-of-life care (a setting in which benefits and risks may be perceived differently).

- Considered that, by improving pain control, ketamine could help to address some of the health need of this group of palliative care patients and may also provide a health benefit to their family and whānau by reducing associated distress.

Discussion

Māori impact

9.6. The Committee considered that Māori are less likely to access palliative care services than non-Māori especially in rural areas, and that private payment of unfunded medicines used in hospices would currently exacerbate medicines access inequities for Māori. The Committee considered that home-based palliative care is more likely to occur for, and may be preferred by, Māori patients and noted that there has been an increase in home-based palliative care due to the COVID-19 pandemic. The Committee considered these cultural differences in end-of-life care.

Discussion

9.7. The Committee noted that ketamine is currently funded in Section H of the Pharmaceutical Schedule without restriction for hospital use. The Committee noted that an application for ketamine for emergency use in rural communities has been ranked as an option for investment. The Committee noted that ketamine is a Class C4 controlled drug (CD), that it is approved by Medsafe for anaesthesia and to supplement low-potency agents such as nitrous oxide, and that its use for palliative care patients with intractable pain not adequately controlled with opioids *is off-label*. The Committee considered that funding ketamine for use in the palliative care setting, outside its Medsafe approved indication, was of little concern as many medicines used in palliative care are off-label and there is an extensive clinical understanding of ketamine.

9.8. The Committee noted the extensive history and clinical advice regarding ketamine for palliative care including recommendations from the Analgesics Subcommittee and PTAC (refer to the Application Tracker for full detail). The Committee noted that, most recently, the Analgesics Subcommittee in December 2019 had recommended that ketamine be funded for this indication under Special Authority, and that PTAC supported this recommendation in February 2020.

9.9. The Committee noted that pain is present in 20-50% of those with cancer, in 80% of people with advanced cancer, and considered that inadequately controlled (intractable) pain is present in up to 20% of people nearing the end of their life. Members considered that this is present in a smaller proportion of people in New Zealand than what is reported in some international studies (eg Are et al. J Surg Oncol. 2017;115:637-41; Solano et al. J Pain Symptom Manage. 2006;31:58-69; Van den Beuken-van Everdingen et al. J Pain Symptom Manage. 2016;51:1070-1090.e9). The Committee considered that pain management for patients nearing the end of their life is often suboptimal due to several contributing factors, including a lack of access to specialist services and advice, fears of medicine abuse and side effects, and the cost to hospices for providing unfunded medicines in the community. The Committee considered that intractable pain is challenging to manage due to the multimodal causes of pain and distress (nociceptive, ischaemic, neuropathic pain) and the fact that simple analgesics and opioids may not be effective for many patients, thereby necessitating admission to an inpatient unit for pain management.

9.10. The Committee considered that palliative care patients have a high health need and that seeing a loved one suffering can have a large impact on family/whānau, causing great distress.

9.11. The Committee considered that Māori are less likely to access palliative care services than non-Māori, especially in rural areas, and that private payment of unfunded medicines used in hospices would currently exacerbate medicines access inequities for Māori. The Committee considered that the same access inequities could apply for Pacific peoples.

9.12. The Committee noted that there are few medication options available to manage neuropathic or ischaemic pain in the palliative setting. The Committee noted that the vast majority of available options are only in oral forms, which is not always suitable for people nearing the end of their life who frequently lose the ability to swallow or for whom metabolism and absorption is disrupted as a result of the disease process. The Committee noted that hospices are community organisations and have little or no access to intravenous forms of anti-neuropathic agents. The Committee considered that the alternative option to manage intractable pain in palliative care would be to provide high-dose medications which would likely result in excessive sedation for the patient, which would be detrimental for interactions with family and loved ones. The Committee considered that the only present potential alternative for managing intractable pain was methadone, a strong opioid used in the management of intractable pains (such as ischaemic or neuropathic pain) but which is not always effective. The Committee considered that its administration is complex in the palliative care setting; there is limited expertise in its use and thus a reluctance to use it in community in subcutaneous form.

9.13. The Committee noted that ketamine is reserved for intractable pain in palliative care that has not responded fully to opioids and/or adjunct analgesics such as steroids, anti-epileptics (including gabapentin/pregabalin), muscle relaxants, bisphosphonates, or anti-depressants. Members considered it likely that ketamine would be a niche use as a third-line or fourth-line treatment which would be targeted to those patients for whom there has been an insufficient response from presently funded analgesics and adjuvants. The Committee considered that ketamine would likely be used in conjunction with opioids, and potentially other adjuncts. The Committee considered that the adverse psychomimetic effects of ketamine are able to be managed with a benzodiazepine or haloperidol.

9.14. The Committee considered that ketamine would likely be given as intermittent burst therapy for most patients, although in some cases it may be given as a continuous infusion. The Committee noted that ketamine interacts with receptors in the pain cascade reducing neuronal hyper-excitability and that the principle behind burst therapy is to reset these pain pathways, thereby facilitating an improved response to opioid analgesics. The Committee considered that there is reluctance to use ketamine long-term as there is no evidence of long-term benefit. The Committee noted that there is no oral ketamine formulation, however, noted that anecdotally, ampoules are reported to be used as oral treatment internationally. Members noted that the Palliative Care Formulary (version 7) references case reports of oral ketamine for intractable pain (eg Broadley et al. Palliat Med. 1996;10:247-50; Kotlińska-Lemieszek et al. J Pain Symptom Manage. 2004;28:100-2).

9.15. The Committee considered that most infusions for palliative care patients are given as an inpatient, in a hospice community inpatient unit, but noted that there has been an increase in home-based palliative care (as opposed to in hospice) due to the COVID19 pandemic. The Committee considered that home-based palliative care is more likely to occur for, and may be preferred by, Māori patients and Pacific patients. The Committee considered that home-based management was complex; however, that this could include continuation of treatment with ketamine for palliative care following initiation of treatment as an inpatient. The Committee considered that infusion-related costs in the community would likely be unchanged if ketamine were funded for this use, as most

palliative care patients are already receiving a continuous subcutaneous infusion (CSCI) or being considered for one, therefore the daily nurse visitation already occurs.

9.16. The Committee considered that it was difficult to estimate the number of patients who would access ketamine in palliative care, as usage ranges from two to three patients per year in some hospices to over 60 per year in a hospice regularly using it. The Committee considered that 75 patients per year was a reasonable estimate for Pharmac to use.

9.17. The Committee considered that there is evidence to support that idea that effectively managing pain in people nearing the end of their life leads to better quality of life (QOL) for patients and their family/whānau (eg Temel et al. N Engl J Med. 2010;363:733-42). The Committee considered that the key outcome for this population was improvement in pain control.

9.18. The Committee noted that a key publication for ketamine in this setting comes from the randomised, double-blind, placebo-controlled study of burst ketamine therapy vs placebo in 185 patients (Hardy et al. J Clin Oncol. 2012;30:3611-7), which reported no benefit of ketamine over placebo and had been reviewed previously by PTAC and by the Analgesics Subcommittee. The Committee noted that study was criticised for enrolling a general population with pain scores that were not very high.

9.19. The Committee considered that its views of the evidence could be summarised as follows:

- Research in palliative care is challenging. There are few randomised controlled trials, and adequately powered studies are rare, and as such, the evidence base for medical management in palliative care is limited in terms of strength and quality. Evidence in this area is mostly based upon case reports, retrospective studies, and uncontrolled studies.

- The evidence base for ketamine for intractable pain often includes contradictory results, is limited by differences between study analgesic regimens (eg. use of intrathecal ketamine or including patients who were not receiving opioids), and ketamine side effects that may undermine blinding of treatment.

- Case reports of ketamine for intractable pain report improvement in pain control with ketamine, with benefits lasting weeks or months for some patients given burst therapy but are unable to consistently determine the characteristics of responders.

- Clinical expert opinion considers ketamine to be a reasonable option for patients nearing the end of their life with intractable pain that is not responsive to opioids or adjuvant analgesia. However, the evidence for ketamine in palliative care lacks long-term data for safety and efficacy, and data for the use of repeat treatments with multiple episodes of burst therapy over time, is unclear.

- Ketamine has well known side effects (eg. abnormal liver function, urinary issues and psychomimetic side effects) that can be monitored for, anticipated and managed in palliative care. The Committee considered that some side effects may be better tolerated in someone who is receiving care at the end of their life than a person not at the end of their life.

9.20. The Committee considered that there is a specific population with intractable pain in palliative care who have a high unmet health need and that many of these patients may benefit from ketamine based on clinical experience and opinion, although those patients

would be hard to identify prospectively. The Committee considered that this high unmet health need was the key driver in its consideration of ketamine for intractable pain in palliative care.

9.21. On balance, the Committee considered that the clinical evidence suggests administering ketamine for a short duration in this patient group would be reasonable due to the high health need. The Committee considered that ketamine may also provide a health benefit to family and whānau by reducing distress.

9.22. The Committee noted that ketamine is a potential drug of abuse. The Committee considered that funding ketamine for intractable pain in palliative care was unlikely to increase the risk of diversion and considered this was a minor risk which would be low with the use of burst therapy. The Committee considered that no additional monitoring was required to manage the risk of diversion in this setting.

9.23. The Committee noted that, if funded under Special Authority for palliative care, ketamine would be able to be accessed via prescription in the community. However, the Special Authority would concurrently preclude timely access in some situations where prescription is less suitable, due to the Pharmaceutical Schedule rules (eg in rural locations, where after-hours access is needed, or where palliative care services may prefer to maintain an available supply such as acutely in the hospice in-patient situation). The Committee noted that enabling access for hospice use but not community access would add to inequities and considered it important to enable funded access to ketamine for the intended population of eligible patients both in hospice and in the community.

9.24. The Committee noted the variation in use of ketamine at hospices around the country and considered there may be slippage in some settings, such as some patients in aged residential facilities (ARC) who would be considered terminally ill, or in rural areas under non-specialist palliative care doctors. However, members noted that there has not been increased use in some hospices where ketamine is supplied by the local DHB.

9.25. The Committee considered that the decision to commence ketamine for the treatment of palliative care patients in the community with intractable pain not adequately controlled with opioids would be made by, or under the guidance of, a palliative care specialist or other specialist working in a palliative care setting, such as a GP specialist working in a hospice. The Committee noted that in some community settings GPs may be comfortable prescribing ketamine in collaboration with a palliative care specialist. The Committee therefore considered that appropriate access to funded treatment with ketamine could be managed by requiring endorsement by a palliative care specialist or relevant specialist, or relevant practitioner on the recommendation of a palliative care specialist or relevant specialist, although deferred to Pharmac staff to ensure that the Schedule rules would not hinder access for patients eligible to receive funded treatment with ketamine.

9.26. 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 community use in palliative care patients with intractable pain not adequately controlled with opioids. 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	Those nearing the end of their life with intractable pain not responsive to usual analgesia (including strong opioids) – includes those with escalating need for high dose opioids.
Intervention	**Ketamine continuous infusion (in less common instances - ~20%)** 1 to 2.5 mg/kg per 24 hours for a maximum of 1 week. **Ketamine burst therapy (in most instances - ~80%)** Treatment duration of 3 to 5 days Low starting dose of 25 mg in some patients eg frail elderly, otherwise initial dose of 50 or 100 mg/24 hr, 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.
Comparator(s)	Best supportive care
Outcome(s)	Improved management of pain and HRQOL

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.

10. Lidocaine hydrochloride 10% subcutaneous (SC) infusion for terminally ill patients whose (mainly neuropathic) pain is not controlled, and the intravenous (IV) route is not appropriate

Application

10.1. The Committee reviewed the clinician application for lidocaine hydrochloride 10% (referred to herein as lidocaine 10%) for subcutaneous (SC) infusion terminally ill patients whose (mainly neuropathic) pain is not controlled, and the intravenous (IV) route is not appropriate.

10.2. The Committee noted that Pharmac staff sought advice from palliative care specialists in late 2021 to help inform the assessment of this application for lidocaine 10% for SC infusion.

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

Recommendation

10.4. The Advisory Committee **recommended** that lidocaine 10% be listed in Section B and Section H of the Pharmaceutical Schedule for the treatment of terminally ill patients whose (mainly neuropathic) pain is not controlled, and the IV route is not appropriate with a **high priority**, within the context of analgesic, anti-emetic, and anaesthetic treatments, subject to the following endorsement:

> Lidocaine – Subsidy by endorsement
> Subsidised only if endorsed by a palliative care specialist, relevant specialist, or relevant practitioner on the recommendation of a palliative care specialist or relevant specialist, where other neuropathic agents haven't been effective.

10.5. In making this recommendation, the Committee considered:

- The high health need of palliative care patients with uncontrolled pain and the severe impact on their family/whānau.

- The limited evidence available to suggest that lidocaine 10% provides an improvement in pain for patients with uncontrolled pain in the context of end-of-life care.

- The suitability benefit of the lower volume of lidocaine 10% over currently funded high volume 1% and 2% preparations in reducing the impact on the healthcare system and improving quality of life for the patient and their family/whānau.

Discussion

Māori impact

10.6. The Committee noted that no direct evidence was identified on the impact of uncontrolled pain in Māori in palliative care. However, it was noted that there is evidence that Māori are disproportionately affected by cancer (Ministry of Health. Cancer. 2018) and therefore members considered that Māori may be more likely to suffer cancer-related pain in the palliative care setting. The Committee also considered that funding of lidocaine 10% would allow for improved symptom control at home, thereby reducing acute admissions and allowing more time with family/whānau.

Discussion

10.7. The Committee noted that the original funding application was for the listing of lidocaine 10% in Section H of the Pharmaceutical Schedule only, however the Committee deemed it appropriate to extend this consideration to Section B (ie funding in the community setting) in order to reach the intended population group.

10.8. The Committee noted that the management of pain is one of the cornerstones of effective palliative care, with neuropathic pain often deemed the most severe of all persisting pains. It was noted that the severity of neuropathic pain is not usually related to the amount of damage, ie 'trivial' lesions can manifest severe pain. The Committee noted that causes for neuropathic pain may include, but is not limited to, peripheral nerve damage (post-surgical, post-trauma or compression), herpetic nerve invasion, amputation, chronic regional pain syndrome, nerve root injury (traumatic avulsion, post-spinal surgery), arachnoiditis, spinal cord injury/disease, stroke, diabetes, or chemotherapy (eg vincristine, oxaliplatin, taxanes, cisplatin) (The Palliative Care Handbook. 2019).

10.9. The Committee considered that the number of palliative care patients requiring lidocaine SC infusions for pain that is not controlled is difficult to quantify, however that this number is small (approximately 185-440 patients per year). It was noted that patient number estimates vary regionally throughout New Zealand.

10.10. The Committee considered that a high health need exists for patients in the end of life setting with uncontrolled neuropathic pain. The Committee considered that, for such patients, standard oral medications for neuropathic pain may not be effective or tolerated. The Committee noted that opioid-refractory pain is distressing for patients because it is notoriously difficult to treat, with patients describing their neuropathic pain as burning, cutting, stabbing, sharp/shooting, and/or crushing (Sharma et al. J Pain Symptom Manage. 2009;37:85-93; The Palliative Care Handbook. 2019).

10.11. The Committee noted that lidocaine 1% and 2% preparations are currently funded and open-listed in both Section B and Section H of the Pharmaceutical Schedule.

However, it was noted that given the low concentration of these preparations, a higher volume of product is required to reach the desired dose, resulting in the use of multiple syringe drivers. The Committee noted that opioids are also used for pain in palliative care, although their use is hampered by side effects such as nausea, vomiting, bowel dysfunction, urinary retention, pruritus, and sedation. The Committee noted that chronic neuropathic pain, particularly when it results from progressive disease such as malignancy, may be unresponsive to opioids (Sharma et al. J Pain Symptom Manage. 2009;37:85-93).

10.12. The Committee noted that when an individual requires palliative care their family/whānau can experience substantial stress, increased depression and anxiety, as well as a lower quality of life compared to the general population (Gotze et al. Eur J Cancer Care. 2018;27Gotze et al. Eur J Cancer Care. 2018;27). The Committee considered that seeing a family/whānau member with uncontrolled pain, especially at the end of their lives, adds to these impacts and may increase the grief experienced with bereavement. Additionally, the Committee noted that the immediate onset of relief from pain lessens the psychological stress on the patient and family/whānau and may help the physician develop a better rapport with the patient, allowing for effective psychological counselling and support (Sharma et al. J Pain Symptom Manage. 2009;37:85-93). The Committee considered that access to improved symptom relief at home leads to less admissions to hospital and/or hospices, thus allowing for improved quality time for family/whānau to be together.

10.13. The Committee noted that people living with dementia may be disproportionately impacted by uncontrolled pain in palliative care as these individuals, by virtue of cognitive impairment, may not be able to validly report either the presence of pain, or the level of pain they are experiencing. The Committee noted that there is evidence that those with dementia are likely to be prescribed up to 50% less analgesia in acute hospital settings than those with comparable needs without a dementia diagnosis (The Palliative Care Handbook. 2019).

10.14. The Committee noted that lidocaine provides anaesthesia at various sites in the body by blocking conduction in nerve axons in the peripheral nervous system (Lidocaine hydrochloride injection SPC 2021). The Committee noted that the lidocaine 10% ampoule (5 ml) or 10% prefilled syringe (500 mg/5 ml) for SC infusion are not currently approved by Medsafe, and that the supplier of Xylocard 500 (AstraZeneca) has not submitted an application to Medsafe to date. The Committee noted that multiple palliative care specialists and various clinical guidelines indicated that lidocaine 10% for SC infusion would be used at a dose of 0.5-2 mg/kg/h, starting at 0.5 mg/kg/h and titrated as necessary. The Committee noted that treatment would be administered short-term (burst therapy) with durations of 1-3 days (ideally 24-72 hours on the effective dose), and, in rare cases, run for a few weeks.

10.15. The Committee considered that the decision to commence lidocaine for the treatment of palliative care patients with uncontrolled pain would be made by, or under the guidance of, a palliative care specialist. The Committee therefore considered that appropriate access to funded treatment with lidocaine 10% could be managed by requiring endorsement by a palliative care specialist, or relevant practitioner on the recommendation of a palliative care specialist, although deferred to Pharmac staff to ensure that the Schedule rules would not hinder access for patients eligible to receive funded treatment with lidocaine. The Committee considered that lidocaine is also currently used in acute pain at lower concentrations (1% and 2%) under strict protocols and that this endorsement would only apply to the higher concentration (10%) for use in palliative care.

10.16. The Committee noted that the health benefit of lidocaine is well established given that the 1% and 2% formulations are currently funded and used in palliative care patients with uncontrolled pain. The Committee reviewed a systematic review and meta-analysis assessing the effects of lidocaine on cancer pain in adults, which found that lidocaine infusions at a dose of 4-5 mg/kg over 30-80 minutes provides a significant benefit and achieved >50% reduction in cancer pain compared with placebo (Lee et al. J Palliat Med. 2019;22:326-334). The Committee considered that lidocaine 10% would benefit a very small number of people with terminal illnesses who have tried multiple other analgesics at high doses without symptomatic relief. The Committee considered that this may include, but not be limited to, those with complex pain which is poorly responsive to opioids/other analgesic adjuvants or in which opioids/other analgesic adjuvants are poorly tolerated, patients at risk of hyperalgesia, acute hyperalgesia, and neuropathic pain.

10.17. The Committee considered that lidocaine 10% for SC infusion provides a suitability benefit over the currently funded 1% and 2% preparations. The Committee considered that the availability of a higher concentration of lidocaine would allow for the administration of a smaller volume of product via a single syringe driver, without the need for additional syringe drivers. It was considered that up to four syringe drivers may be required at a time to increase the dose to sufficient therapeutic levels using the currently funded 1% and 2% formulations. The Committee considered that this may result in multiple SC lines being attached to the patient, which can be cumbersome and unpleasant for them and their family/whānau. The Committee considered that the availability of the 10% formulation would simplify the administration of lidocaine infusions, thereby reducing pressure on nursing staff, minimising disruption to the patient, and reducing the infusion equipment required during this process, making it available for use in other patients. The Committee also considered that a reduction in the number of syringe drivers required may also improve the patient and family/whānau quality of life by allowing patients to transition more easily toward home-based palliative care.

10.18. The Committee considered that the cost of funding lidocaine 10% is likely to be minimal given the small patient numbers. The Committee considered it would take two nurses 15 minutes to prepare each lidocaine syringe, and that any time saving estimate should be based on this assumption. The Committee considered that with current 1% and 2% formulations, the administration of 4 syringe drivers every 12 hours would equate to 4 hours of nursing time per 24 hours. The Committee therefore considered that, if lidocaine 10% were to be funded, the reduction in syringe driver use would result in less nurse time spent preparing, administering, and monitoring lidocaine infusions, therefore reducing costs to the healthcare system. Members also considered the potential for increased adverse events and drug error in funding a preparation of a higher concentration, which may result in additional healthcare expenditure.

10.19. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for lidocaine 10% if it were to be funded in New Zealand for terminally ill patients whose (mainly neuropathic) pain is not controlled. 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	Terminally ill patients whose (mainly neuropathic) pain is not controlled, and the IV route is not appropriate.

Intervention	0.5-2 mg/kg/hr lidocaine 10% via subcutaneous infusion. Dose would be started at 0.5 mg/kg/hr and titrated as necessary, with the average amount of time on treatment being 72 hours.
Comparator(s) (NZ context)	Lidocaine 1% and 2% preparations.
Outcome(s)	Simplified method of lidocaine infusion administration, resulting in less pressure on nursing staff, less disruption to the patient and reduced use of infusion equipment. The analgesic effect is expected to be the same as lidocaine 1% and 2% preparations.

Table definitions:
Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)
Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).
Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).
Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

11. Levetiracetam (subcutaneous) - Monotherapy or adjunctive therapy for seizure control in palliative care setting [P-001527]

Application

11.1. The Committee reviewed the clinician application for the use of subcutaneous levetiracetam for monotherapy or adjunctive therapy for seizure control for palliative care patients in the community setting.

11.2. The Committee noted that Pharmac staff had intended for the application be taken to PTAC for advice in May 2020, however, this had to be deferred due to the need to undertake other work directly associated with the COVID-19 response in 2020.

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

Recommendation

11.4. The Committee **recommended** that subcutaneous (SC) levetiracetam (inj 100 mg per ml, 5 ml vial) be listed in Section B of the Pharmaceutical Schedule with a **medium priority**, within the context of analgesic, anti-emetic and anaesthetic treatments, subject to the following endorsement:

> LEVETIRACETAM SUBCUTANEOUS – Subsidy by endorsement
> Subsidised only if endorsed by a palliative care specialist or neurologist, relevant specialist, or relevant practitioner on the recommendation of a palliative care specialist, neurologist, or relevant specialist.

11.5. In making this recommendation, the Committee considered:

- The very high health need of patients in a palliative care or hospice setting who experience or are at risk of seizures and can no longer take oral medications and for whom current treatment options have sedative effects

- That seizures in palliative care substantially impact the quality of life of the family and whānau of palliative care patients, leading to wider stress and distress

- That there is limited evidence from small observational studies that are subject to a high risk of bias and included confounding variables, which suggests that SC levetiracetam would be efficacious and tolerable for this population

- That SC levetiracetam may be less sedating than, and its SC formulation may provide a benefit over, other anti-seizure medications whose administration routes may be unsatisfactory in a palliative care situation

- That SC levetiracetam appears to be a cost-effective option for managing seizures in this population.

Discussion

Māori impact

11.6. The Committee considered that Māori are less likely to access palliative care services than non-Māori especially in rural areas, and that private payment of unfunded medicines used in hospice would currently exacerbate medicines access inequities for Māori. The Committee considered that home-based palliative care is more likely to occur for, and may be preferred by, Māori patients and Pacific patients and noted that there has been an increase in home-based palliative care due to the COVID19 pandemic.

Discussion

11.7. The Committee considered that seizure management is an important issue for palliative care, as seizures are often associated with brain metastases or tumours in patients who are receiving palliative care for reasons other than epilepsy. The Committee considered that seizures in the palliative care setting are very distressing for the patient, their family and whānau, and members considered that, based on clinical experience, it affects their quality of life.

11.8. The Committee did not identify any specific impact of seizures on the health outcomes of Māori or other groups experiencing health disparities, however, the Committee considered that Māori are less likely to access palliative care services than non-Māori especially in rural areas, and that private payment of unfunded medicines used in hospice would currently exacerbate medicines access inequities for Māori, although acknowledged this added cost may present issues for all patients in hospice palliative care. The Committee considered that the same access inequities could apply for Pacific peoples. The Committee also considered that home-based palliative care is more likely to occur for, and may be preferred by, Māori patients and Pacific patients. The Committee noted that there has been an increase in home-based palliative care (as opposed to in hospice) due to the COVID19 pandemic.

11.9. The Committee noted that there are no subcutaneous formulations of the most frequently used oral antiepileptic drugs (AEDs) and no non-sedating AEDs currently available or funded. The Committee noted that using intravenous (IV) lines for treatment administration can be challenging in the palliative population and that current treatment

options require a syringe driver for administration. The Committee considered that subcutaneous (SC) midazolam is the most common funded treatment option for managing seizures in palliative care once the oral route is lost, often requiring higher doses given with a syringe driver to achieve seizure control. The Committee noted that IV phenobarbitone and SC clonazepam may also be used, although phenobarbitone is highly sedative and is therefore reserved as a last resort. The Committee considered that these options are sedative at a time when sedation may not be desired, and they may not be sufficiently effective in controlling seizures.

11.10. The Committee considered that there remained a very high unmet need based on clinical experience, currently available treatment options for seizure control in palliative care, and the severe impact of seizures on the palliative patient, their family and whānau.

11.11. The Committee noted that levetiracetam tablets and oral liquid are funded in Section B (for community use) and Section H (for hospital use) of the Pharmaceutical Schedule without restriction. The Committee noted that levetiracetam inj 100 mg per ml, 5 ml vial is funded in Section H (Hospital) of the Pharmaceutical Schedule without restriction. The Committee noted that, while levetiracetam is available in oral formulations, there is only one Medsafe-approved brand of levetiracetam for intravenous (IV) injection and that subcutaneous use of levetiracetam would be off-label (Medsafe data sheet).

11.12. The Committee noted that SC levetiracetam is recommended in Scotland (SMC, September 2006) as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from four years of age with epilepsy, and that SC levetiracetam is an alternative when oral administration is temporarily not feasible, in patients for whom levetiracetam is an appropriate anticonvulsant. The Committee noted there was no evidence of consideration of SC levetiracetam in Australia (PBAC), Canada (CADTH) or England and Wales (NICE).

11.13. The Committee noted that oral levetiracetam is currently prescribed for seizure prevention in palliative care patients at risk of or with a previous history of seizure due to brain metastases or brain tumours. The Committee noted that SC doses range from 250-4000 mg per 24 hours as a continuous subcutaneous infusion (CSCI) and that levetiracetam has a 1:1 ratio for conversion from oral to SC dosing. The Committee noted that SC levetiracetam requires a separate syringe driver due to its variable compatibility with other medicines, would require a large volume syringe for moderate to high doses, and would ideally be diluted to help prevent site reactions.

11.14. The Committee noted that SC levetiracetam may be used as monotherapy or adjunctive therapy and may be started de novo as a CSCI. The Committee considered that, if funded, SC levetiracetam would mostly be used following prior treatment with oral levetiracetam in patients who have lost the ability to swallow. The Committee considered that it would also be used as an adjunctive treatment where other AEDs (eg high-dose midazolam) were unable to control seizures and might be used de novo SC therapy in a small number of cases where seizure onset requires rapid control. The Committee considered that the availability of SC levetiracetam would allow a smooth transition from oral to SC use when a palliative care patient can no longer swallow and that this was likely to be a preferable option for seizure management from the perspective of family and whānau, however, considered that it would not be appropriate to require patients to have taken oral levetiracetam prior to accessing funded SC levetiracetam.

11.15. The Committee noted the evidence for SC levetiracetam in palliative care from a retrospective chart review of 20 patients, of which 18 had a primary brain tumour or

brain metastasis, who received SC levetiracetam at a mean dose of 95.8 mg per hour (tandfonline.com/doi/full/10.3109/15360288.2014.959234). The Committee noted that 75% received an oral AED prior to receiving SC levetiracetam and that the median duration of SC levetiracetam treatment was five days (range one to 22 days). The Committee noted that 80% of patients had no further seizures, that one patient discontinued the infusion due to deteriorating status epilepticus, and that minor infusion site reactions were reported in four patients.

11.16. The Committee noted a literature review and prospective audit of SC levetiracetam for the management of seizures at the end of life which was published in 2018 (Sutherland et al. BMJ. 2018;8:129-136) and the updated literature review and retrospective audit published in 2021 which incorporated the earlier findings (Sutherland et al. J Palliat Med. 2021;24:976-81).

11.16.1. The Committee noted that the Sutherland et al. literature review contained 12 case reports, eight case series and one audit, including 108 patients who received SC levetiracetam CSCI and 12 patients who received SC boluses or a SC infusion. The Committee noted that doses ranged from 250-4000 mg per 24 hours and the treatment duration ranged from one to 55 days. The Committee noted that 110 patients continued treatment with SC levetiracetam until death and that six improved and were able to revert to oral AEDs. The Committee noted that seven patients had possible seizure activity while on SC levetiracetam and a further 53 patients who received concomitant midazolam had no noted seizure activity, however, the Committee considered that concomitant use of midazolam was a confounding variable. The Committee noted that seven patients had infusion site reactions.

11.16.2. The Committee noted that the Sutherland et al. retrospective audit (2021 publication) reported on 19 patients over a one-year period. The Committee noted that 17 patients had been on levetiracetam orally prior, 17 patients continued treatment until death, 2 patients improved and reverted to oral therapy, and there were no adverse events or site reactions.

11.16.3. The Committee noted that the Sutherland et al. prospective audit (2018 publication) reported on 20 patients who received CSCI levetiracetam over a one-year period. The Committee noted that the treatment duration ranged from 21 hours to 26 days The Committee noted that 19 patients had been on oral levetiracetam prior, and 13 patients had concomitant administration of other AEDs. The Committee noted that seven patients were reported to have seizures, myoclonus or twitching on CSCI levetiracetam which was resolved by increasing the levetiracetam dose or introducing other AEDs. The Committee noted that 12 patients continued treatment until death and three patients improved and reverted to oral therapy. The Committee noted that one patient had a site reaction, and one patient had a sterile abscess after 25 days of treatment.

11.16.4. The Committee noted that both the duration of SC levetiracetam and the doses used ranged broadly. Based on this evidence, the Committee considered it was reasonable to assume a mean duration of less than 10 days treatment and a mean dose of 1600 mg per 24 hours.

11.17. The Committee also noted evidence from a regional multicentre audit of 26 adult patients requiring anticonvulsant medication but unable to take oral preparations, of which 14 received SC levetiracetam (Cran et al. BMJ Support Palliat Care 2018;8:A73-4), a case series of six palliative care patients with epileptic seizures who received SC levetiracetam (Mas-Sese et al. Neurologia (Engl Ed) 2021;36:474-5), and the following clinical guidelines provided by the applicant and by palliative care specialists:

- Specialist Palliative Care Audit and Guidelines Group (SPAGG, UK): Clinical Guideline for Commencing Levetiracetam via Syringe Driver Version 1.0. 2018

- Our Lady's Hospice and Care Services, Ireland. The use of subcutaneous levetiracetam in palliative medicine. 2016

- Scottish Palliative Care Guidelines (NHS Scotland)

- Counties Manukau DHB levetiracetam guideline in palliative care (not available online)

- Harbour Hospice North Shore subcutaneous levetiracetam guideline (not available online)

- Waikato DHB guideline: Management of seizures

11.18. The Committee considered that the available evidence for SC levetiracetam was of poor strength and low quality, being mostly observational data at high risk of bias but that this was not unusual for palliative care research, which has inherent challenges that make randomised controlled or comparative trials unlikely to be feasible. The Committee considered that the evidence supported efficacy and tolerability of SC levetiracetam for palliative care patients experiencing or at high risk of seizures although there was no evidence to suggest that SC levetiracetam would be any more effective than other AEDs. The Committee noted that the key adverse effect is the risk of a minor skin reaction at the infusion insertion site, which can occur with other AEDs. Overall, the Committee considered that seizure control and the lack of sedation with SC levetiracetam would likely provide benefits for the target patient population of palliative care patients with seizures at the end of life who are unable to swallow and prefer not to be sedated, and that it would also provide psychosocial benefits for family and whānau.

11.19. The Committee considered that the number of patients who might use SC levetiracetam was uncertain and that Pharmac had sought advice from palliative care specialists regarding this to inform its estimates. The Committee considered that Pharmac's estimate of about 650 patients per year (based on assumptions regarding the proportions of patients with primary brain tumours and with metastatic brain lesions in palliative care, and negligible use outside these groups) was likely reasonable. The Committee considered that the mean duration of SC levetiracetam treatment would be less than 10 days.

11.20. The Committee considered that SC levetiracetam would likely replace all other AEDs especially midazolam, although noted that SC levetiracetam may be used in combination with midazolam where there is insufficient seizure control with SC levetiracetam alone.

11.21. The Committee considered that SC levetiracetam may increase nursing time and material costs in cases where administration requires a larger syringe, a different driver (T60), or two syringes with the dose split between them.

11.22. The Committee considered it would be important for SC levetiracetam to be accessible after hours and in rural locations. The Committee considered that no Special Authority criteria were required to manage fiscal risks, given the low cost of SC levetiracetam for the small population of patients who would be targeted. The Committee considered that the decision to commence SC treatment for seizures in palliative care patients would be made by, or under the guidance of, a palliative care specialist or neurologist. The Committee therefore considered that appropriate access to

funded treatment with SC levetiracetam could be managed by requiring endorsement by a palliative care specialist or neurologist, or relevant practitioner on the recommendation of a palliative care specialist or neurologist, although deferred to Pharmac staff to ensure that the Schedule rules would not hinder access for patients eligible to receive funded treatment with SC levetiracetam.

11.23. The Committee noted that a reduction in seizure frequency is used as an outcome for trials of seizures in epilepsy and considered that cessation of seizures would also be a relevant outcome for Pharmac's assessment of SC levetiracetam in this palliative population.

11.24. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for SC levetiracetam if it were to be funded in New Zealand for seizure control in 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	Palliative care patients experiencing seizures or at risk of experiencing seizures who can no longer take oral anti-seizure medications (usually levetiracetam)
Intervention	Levetiracetam 500 – 4000 mg over 24 hours (via continuous subcutaneous infusion). (Mean 1600 mg based on the two audits by Sutherland et al.) If a patient transitions from oral levetiracetam to subcutaneous administration, dose conversion is 1:1.
Comparator(s)	Midazolam SC 10-60 mg per 24 hours (or clonazepam SC 1-4 mg per 24 hours in a small proportion of patients).
Outcome(s)	Improved control of seizure activity.
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.	

11.25. The Committee considered that Pharmac could provide a copy of this record to the Neurology Advisory Committee for review.

12. Methylnaltrexone bromide subcutaneous injection for the treatment of opioid induced constipation outside of palliative care

Application

12.1. The Committee reviewed the application for methylnaltrexone bromide in the treatment of opioid induced constipation.

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

Recommendation

12.3. The Committee **recommended** that methylnaltrexone bromide for opioid induced constipation be listed with a **medium priority** within the context of analgesic, anti-emetic and anaesthetic treatments subject to the following Special Authority criteria:

Initial application — (Opioid induced constipation) from any relevant practitioner on the recommendation of a specialist.

Approvals valid for 12 weeks for applications meeting the following criteria:

1. Patient has opioid induced constipation; and
2. Either
   - 2.1. Oral and rectal laxative treatments have not induced laxation within 72 hours; or
   - 2.2. Oral and rectal treatments for opioid induced constipation are ineffective or inappropriate; or
   - 2.3. Patient has been hospitalised for opioid induced constipation.

Renewal application — (Opioid induced constipation) from any relevant practitioner

Approvals valid for 12 weeks for applications meeting the following criteria:

1. Patient continues to experience opioid induced constipation; and
2. Oral and rectal treatments for opioid induced constipation continue to be ineffective or inappropriate; and
3. The initial dose of methylnaltrexone bromide was successful in inducing laxation within 24 hours of administration
4. Patient is receiving methylnaltrexone bromide injections no more than once every 48 hours; and
5. Patient does not receive more than 2 renewals.

12.4. The Advisory Committee made this recommendation based on the high health need for patients with opioid induced constipation, the evidence of benefit of methylnaltrexone bromide for this patient population, and the more favourable suitability, especially compared to enemas or manual disimpaction.

Discussion

12.5. The Committee noted that methylnaltrexone bromide for opioid induced constipation in palliative care was funded in 2018, and that a subsequent application from a clinician requested widened access for funding for all patients experiencing opioid induced constipation, not only those receiving palliative care. The Committee noted that PTAC reviewed this widening of access application in May 2019 and recommended funding methylnaltrexone bromide outside of palliative care with a low priority and recommended that the application be referred to the Gastrointestinal Advisory Committee or the Analgesic Advisory Committee for advice regarding the appropriate Special Authority criteria and the population of patients with the highest health need. The Committee noted that PTAC considered at the time that there would be significant fiscal risk associated with widening access to methylnaltrexone without restriction, due to the large population that may be prescribed methylnaltrexone.

12.6. The Committee also noted that PTAC considered that the patient numbers suggested by the applicant (approximately 50 patients requiring rescue therapy for intractable opioid-induced constipation following trauma or surgery) may be too low, and that there was evidence that methylnaltrexone may provide a benefit in a wider group of non-palliative patients with intractable opioid-induced constipation.

12.7. The Committee noted that opioid induced constipation is characterised by persistently, difficult, infrequent or incomplete defaecation associated with opioid use, and that tolerance to constipation does not develop over time as it does with the nausea, vomiting and sedative effects of opioids. The Committee noted that opioid induced constipation can be associated with abdominal and rectal pain, cramps, bloating, distress, haemorrhoids, bowel perforation, nausea, or faecal impaction which may require manual disimpaction that sometimes requires general anaesthetic. The Committee noted that opioid induced constipation has a negative impact on the patient's

ability to work, health related quality of life, and mental health. The Committee noted that there are multiple laxative options available for patients that are effective for the majority of people but are not specifically targeted to opioid induced constipation.

12.8. The Committee noted that constipation is anticipated for patients initiating opioid treatment and it should be treated early with regular laxatives from initiation to cessation of opioid use. The Committee noted that oral laxatives are sometimes ineffective or not well tolerated, in which case patients may need an enema. The Committee noted that enemas present with their own set of problems, such as the risk of rectal injury from chemical irritation or mechanical trauma, and that they are not suitable for children experiencing opioid induced constipation. The Committee also noted that an estimated 70% of patients are too embarrassed to discuss their opioid induced constipation with their physician, and that only 40-60% of physicians discuss the risk of opioid induced constipation with their patients (Argoff CE. Clin J Pain. 2020;36:716-722Argoff CE. Clin J Pain. 2020;36:716-722).

12.9. The Committee noted the Rome IV diagnostic criteria (C6) for opioid induced constipation, which specifies symptoms associated with constipation associated with initiating, changing or increasing opioid therapy. The Committee noted that these diagnostic criteria demonstrated a high diagnostic accuracy of 81.9% in an observational study of patients with cancer (Davies et al. Pain. 2021;162:309-18). The Committee noted that opioid induced constipation occurs in 41-57% of patients with chronic non-cancer pain (Drewes et al. Scand J Pain. 2016;11:111-22). The Committee noted that dose, frequency, and duration of opioid therapy influence the likelihood of having opioid induced constipation.

12.10. The Committee noted that methylnaltrexone bromide is a peripherally acting mu opioid receptor antagonist (PAMORA) that is administered as a 12 mg (or 0.15 mg/kg for lighter or heavier patients) subcutaneous injection. The Committee noted that methylnaltrexone bromide is a quaternary amine, which does not cross the blood brain barrier and therefore doesn't reverse the opioid analgesic effect. The Committee noted that there are oral PAMORAs available, but none are currently funded in New Zealand. The Committee also noted that methylnaltrexone bromide is FDA approved for use in chronic non-cancer pain.

12.11. The Committee noted the following evidence for use of methylnaltrexone bromide for opioid induced constipation in non-palliative care:

12.11.1. Anissian et al. J Hosp Med. 2012;7:67-72: a randomised, double blind, placebo controlled phase II exploratory study in postoperative orthopaedic patients older than 18 years who had an operation within four to 10 days and are expected to need for opioids for seven days, who were given methylnaltrexone bromide or placebo subcutaneously daily for four or seven days (until opioid treatment cessation or hospital discharge). The Committee noted that there was no primary endpoint specified for this study, and that acute constipation was defined as no bowel movement for 48 hours, or difficult or inability to have a spontaneous bowel movement. The Committee noted that no laxative, enema or promotility agent was given for 48 hours prior to the first dose of methylnaltrexone bromide.

12.11.2. The Committee noted that of the 33 patients who received at least one dose of methylnaltrexone bromide, six patients achieved laxation within 24 hours, and seven patients within 48 hours. The Committee noted that three patients in the treatment group and three patients in the placebo group received rescue laxatives. The Committee noted that the median time to laxation with methylnaltrexone bromide was 15.8 hours versus 50.9 hours with placebo (P=0.02). The Committee also noted that overall treatment

satisfaction was 83.3% in the methylnaltrexone bromide group, versus 53.3% in the placebo group. The Committee noted that adverse event rates were similar between the treatment and placebo group, and that these were mostly gastrointestinal in nature.

12.11.3. Chamberlain et al. Pain Manag. 2020;10:73-85: a *post hoc* analysis of two trials (MNTX 301 and MNTX 302) of patients with advanced illness (with or without cancer) who were treated with methylnaltrexone bromide or placebo for opioid induced constipation. The Committee noted that 36.6% of the patients enrolled in the studies had chronic non-cancer pain, and that most patients were using concurrent laxatives which were continued during the trial period.

12.11.4. The Committee noted that the percentage of responders to methylnaltrexone bromide was 63.8% versus 14.9% in the placebo group for cancer patients, and 59.7% versus 19.7% on placebo for non-cancer patients, within 4 hours of the first dose. The Committee also noted that after 2 or more of the first four doses, 56.9% of cancer patients and 58.1% of non-cancer patients achieved a response compared to 5.3% and 11.3% with placebo, respectively. The Committee noted that the mean number of laxations was statistically significantly higher for the methylnaltrexone treated patients compared to placebo patients, and that the percentage of patients using rescue laxatives was lower.

12.11.5. Patel et al. Intensive Care Med. 2020;46:747-55 the MOTION trial: a multi-centre, double blind, randomised placebo-controlled trial to investigate whether methylnaltrexone bromide alleviated opioid-induced constipation in critical care patients compared to placebo. The Committee noted that patients were adult ICU patients who were mechanically ventilated, receiving opioids and were constipated (had not opened bowels for a minimum 48 hours) despite prior administration of regular laxatives as per local bowel management protocol. The Committee noted that there was no significant difference in time to rescue-free laxation between the groups (HR 1.42; 95% CI 0.82–2.46; p = 0.22). The Committee considered that ICE-related constipation is multifactorial and may not be only related to opioid use.

12.11.6. Liao et al. Drugs Aging. 2021;38:503-511: an analysis of data pooled from four randomised controlled trials of adults diagnosed with opioid induced constipation who received opioids for pain management and who had a terminal illness or chronic non-malignant pain, stratified by age. The Committee noted that methylnaltrexone use did not adversely affect pain control, opioid withdrawal effects, or adverse events while providing effective rescue-free laxation, regardless of age, and the most frequent treatment related adverse events were abdominal pain, flatulence of nausea.

12.11.7. Novak et al. Paediatr Child Health. 2020;27:e105-9: a retrospective study of all children admitted to the Stollery Children's Hospital in Edmonton (Canada) who received either methylnaltrexone or naloxegol for opioid induced constipation. The Committee noted that a total of 27 patients were included in the study (70% palliative care, 15% PICU, and 15% postoperative) and that Kaplan-Meier analysis showed the median time to the first bowel movement after the first dose of either methylnaltrexone or naloxegol was 15.5 hours. The Committee noted that seventeen (63%) patients had laxation within 24 hours of first dose and that no significant adverse events were observed.

12.11.8. Rekatsina et al. Cureus. 2021;13:e16201: systematic review of the existing literature on PAMORAs aimed to study the relative clinical advantages and disadvantages. The Committee noted that 14 of the studies included were relating to methylnaltrexone, six included non-cancer patients, and six studies included both cancer and non-cancer patients. The Committee noted that all studies showed that

methylnaltrexone is well tolerated in treating opioid induced constipation within 4 hours of the first dose in patients with advanced illness and non-cancer pain. The Committee noted that serious cardiovascular adverse events were recorded, including extrasystole, syncope and chest pain, all of which resolved upon discontinuation of methylnaltrexone bromide.

12.11.9. Zhang et al. Pain Ther. 2021;10:165-79: a meta-analysis assessing the efficacy and safety of methylnaltrexone compared with placebo in the treatment of opioid-induced constipation including eight trials with 2034 participants. The Committee noted that the authors did not differentiate between palliative and non-palliative care settings. The Committee noted that methylnaltrexone increased rescue-free bowel movement (RFBM) within four hours after the first dose (eight trials; 1833 participants; risk ratio 3.74, 95% CI 3.02-4.62), RFBM within 24 hours after the first dose (two trials; 614 participants; risk ratio 1.98, 95% CI 1.52-2.58), and RFBM ≥ 3 times per week (three trials; 1,396 participants; risk ratio 1.33, 95% CI 1.17-1.52) and decreased need to take rescue laxatives (three trials; 807 participants; risk ratio 0.73, 95% CI 0.63-0.85). The Committee noted that a considerable number of patients still required rescue laxatives and considered that the symptoms in these patients may not be due only to opioid treatment. The Committee noted two case reports of gastrointestinal perforation with methylnaltrexone use.

12.12. The Committee noted that no opioid withdrawal was reported in any study, and that methylnaltrexone bromide appears to be safe for use with children and the elderly. The Committee also noted that methylnaltrexone bromide is contraindicated in patients with bowel obstruction, postoperative ileus, and acute abdominal pain.

12.13. The Committee noted the following additional studies in relation to methylnaltrexone bromide for the treatment of opioid induced constipation:

12.13.1. Chamberlain et al. J Pain Res. 2021;14:2687-97

12.13.2. Argoff CE. Clin J Pain. 2020;36:716-22

12.14. The Committee noted that overall, the evidence for use of methylnaltrexone bromide for opioid induced constipation came from heterogenous studies with variable definitions of opioid induced constipation, mainly in the setting of chronic non-cancer pain as opposed to in-hospital peri-operative use. The Committee considered that methylnaltrexone bromide is as effective in non-palliative patients with opioid induced constipation as in the palliative care setting, with regard to producing a rescue free bowel movement within four to 24 hours after the first dose.

12.15. The Committee noted that use of methylnaltrexone bromide does not negate the need for rescue laxatives, and that none of the above studies reported on the need for manual evacuations or the impact of methylnaltrexone use on hospital or ICU discharge rates. The Committee considered that funding methylnaltrexone bromide for non-palliative care patients in the community may also decrease hospital visits due to complications related to constipation such as haemorrhoids.

12.16. The Committee noted that the number of patients who would have access to methylnaltrexone bromide if access were to be widened to non-palliative care patients is unknown but considered that there may be approximately 1600 patients per year based on opioid dispensing rates (11% per 1,000; Moore D; Davies P. Report to the Faculty of Pain Medicine. 2018), assuming 12% of opioids are for chronic pain (treatment >6 weeks, hqsc.govt.nz 2022), proportions of patients with opioid induced constipation from the literature (41-57% from Rekatsina et al. 2021) and proportion of patients for which

conventional laxatives are ineffective in (~50%, Kumar et al. Gastroenterol Res Pract. 2014;2014:141737). The Committee considered that if oral PAMORA's were made available, it would make more sense to use these versus other laxatives in patients with no other underlying constipation risk factors. The Committee considered that availability of PAMORA's may facilitate improved patient/physician communication about opioid induced constipation.

12.17. The Committee considered that chronic non-cancer patients with opioid induced constipation present the highest health need, as they will likely be taking opioids for extended periods of time.

12.18. The Advisory 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 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 Advisory 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	Intractable opioid-induced constipation in patients outside of palliative care when oral and rectal treatments are ineffective or unable to be tolerated. (Patient numbers unknown)
Intervention	12 mg subcutaneous injection of methylnaltrexone bromide every alternate day.
Comparator(s) (NZ context)	Either no treatment, or manual disimpaction.
Outcome(s)	Reduced time to bowel movement.

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.