Record of the Analgesic Subcommittee meeting held at PHARMAC and via videoconference on 3 December 2019 (record for web publishing)

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

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

The Analgesic Subcommittee 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.

This Subcommittee meeting record was reviewed by PTAC at its meeting of 20-21 February 2020, the record of which will be available in due course.

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Present from the Analgesic Subcommittee:
Dr Giles Newton-Howes (Chair)
Dr Tipu Aamir (via videoconference)
Dr Rick Acland (via videoconference)
Prof Brian Anderson (via videoconference)
Dr Christopher Jephcott (via videoconference)
Dr Christopher Lynch (via videoconference)
Dr Jane Thomas (via videoconference)
Dr Alana Wilson
Dr Howard Wilson
Dr Janine Winters

Apologies:
None

1. The role of PTAC Subcommittees and records of meetings

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

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

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

1.4. The Analgesic Subcommittee is a Subcommittee of PTAC. The Analgesic Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives:

1.5. Both PTAC Subcommittees and PTAC are statutory advisory committees established by the PHARMAC Board (external to and separate from PHARMAC staff). Both provide objective advice to PHARMAC on community and hospital pharmaceuticals and their benefits, using the PHARMAC Factors for Consideration. PTAC Subcommittees complement and are separate from PTAC; they are not subordinate.

- PTAC Subcommittees provide objective advice within specific therapeutic areas. PTAC Subcommittees are appointed to reflect specialist knowledge and expertise in health needs and treatments within their own therapeutic groups/areas of clinical practice, including the applicability of evidence to clinical funding settings in New Zealand. The Analgesic Subcommittee provides advice in the therapeutic area of analgesics, anaesthetics, and antinausea and vertigo agents.

- PTAC Subcommittees make recommendations, including providing a priority, within their therapeutic groups of interest. The Analgesic Subcommittee recommends with priority within the context of analgesics, anti-emetics and anaesthetics, as within that area of health need and clinical practice.

- PTAC considers Applications or PHARMAC staff proposals across all therapeutic groups in the Pharmaceutical Schedule. It has an overview view of Applications and other items referred to it for clinical advice. PTAC provides and promotes critical

appraisal of strength and quality of evidence, applied rigorously, systematically and consistently across all therapeutic groups.

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

  The Analgesic Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for analgesics, anti-emetics and anaesthetics that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for analgesics, anti-emetics and anaesthetics that differ from PTAC Subcommittees', or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'. PHARMAC considers the recommendations provided by both the Analgesic Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for analgesics, anti-emetics and anaesthetics.

2. Record of previous minutes

2.1. The Subcommittee noted and accepted the record of the previous meeting held on 27 March 2018.

3. Previous action points/recommendations made

3.1. The Subcommittee noted action points made at its previous meetings in March 2018, March 2016, December 2014, September 2013 and April 2010, and the current status of these action points.

3.2. The Subcommittee noted that the proposal for ketamine pre-filled syringes for use in the pre-hospital setting is scheduled for prioritisation by PHARMAC at its December prioritisation meeting. Members noted that this represented an 18-month time from their clinical advice to prioritisation, and that PHARMAC staff advised that this timeframe was due to the volume of high priority applications being processed.

3.3. The Subcommittee noted that PHARMAC had sent correspondence to the Chair of the Australia New Zealand Society of Palliative Medicine (ANZSPM) Aotearoa Committee regarding a funding application for fentanyl sublingual tablets. The Subcommittee considered that this was an appropriate group for PHARMAC to engage with on matters related to palliative care. The Subcommittee considered PHARMAC staff could also contact the Chair of Hospice New Zealand on these matters. The Subcommittee noted that the Ministry of Health Palliative Care Medicines Working Group (PCMWG) was no longer in existence.

4. Correspondence and Matters Arising

Lidocaine gel for intractable rectal pain/tenesmus (widening access)

Application

4.1. The Subcommittee reviewed a clinician application requesting funded access of lidocaine (lignocaine) gel 2%, urethral syringe be widened to include the treatment of intractable rectal pain/tenesmus.

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

Recommendation

4.3. The Subcommittee **recommended** access to lidocaine (lignocaine) gel 2%, urethral syringe be widened to include the treatment of intractable rectal pain/tenesmus with a low priority within the context of anaesthetic treatments. The Subcommittee made this recommendation based on the high unmet health need of patients with intractable rectal pain/tenesmus who may require hospice admission for pain relief, acknowledging that there is poor evidence to support lidocaine gel in this indication and that further evidence is unlikely to be generated.

4.4. The Subcommittee considered that lidocaine (lignocaine) gel 2%, urethral syringe should be listed with the following Special Authority criteria:

LIDOCAINE [LIGNOCAINE] HYDROCHLORIDE
Gel 2%, 10ml urethral syringe
Special Authority for Subsidy
Initial application – (intractable rectal pain) from any relevant practitioner. Approvals valid for 3 months. All of the following:

1. Patient has intractable rectal pain/tenesmus, and
2. Treatment is to be used in palliative care, and
3. Lidocaine gel 2%, 10ml urethral syringe is for rectal administration, and
4. Treatment is for a maximum duration of 3 months.

Discussion

4.5. The Subcommittee noted that lidocaine gel 2%, urethral syringe has been listed with sole supply status since 1 November 2019 and that this resulted in a reduced cost per syringe. The Subcommittee noted that in response to the price reduction, an application had been received from two palliative care practitioners to widen access to meet an unmet clinical need by including the use in rectal pain/tenesmus. The Subcommittee considered that the key question to be addressed was whether access to lidocaine gel 2%, urethral syringe should be widened to include rectal application in the community and hospital settings.

4.6. The Subcommittee noted that rectal tenesmus is the persistent, painful sensation of incomplete evacuation of the bowel that is experienced as distressing, episodic pain between one to six times a day. The Subcommittee noted that rectal pain/tenesmus is an infrequent condition which generally results from an underlying malignancy such as rectal carcinoma and that it can have a significant impact on a person's quality of life. The Subcommittee noted that the overall prevalence of rectal tenesmus is unknown, however, the prevalence in people with recurrent rectal carcinoma is approximately 14%. The Subcommittee noted that some patients may not experience sufficient relief with conventional treatments, in which case their rectal pain/tenesmus is described as intractable.

4.7. The Subcommittee considered that intractable rectal tenesmus is generally a late presenting symptom in the palliative care setting. The Subcommittee considered that in the majority of patients the maximum duration of treatment would be two months in the end of life setting. The Subcommittee considered that if the symptoms were unable to be controlled then the patient would instead be admitted to hospice for pain relief.

4.8. The Subcommittee noted that treatment of the underlying malignancy may be an option for patients who are suitable for surgery, radiotherapy and/or; other treatments for rectal pain/tenesmus may include lumbar sympathectomy, endoscopic laser therapy or

medicines. The Subcommittee noted that medicines such as amitriptyline, bupivacaine, diltiazem, gabapentin, lidocaine, methadone, mexiletine hydrochloride, nifedipine and other opioids may be used either alone or in a combination, with or without other interventions. The Subcommittee noted that some of these medicines are funded for unrestricted use in the community (Section B of the Pharmaceutical Schedule), enabling use in hospice, but that some patients will experience symptoms that are refractory to the funded treatment options. The Subcommittee noted that there is no topical anaesthetic funded for this use in the community setting.

4.9. The Subcommittee noted that bupivacaine hydrochloride solution for injection is listed in Section H of the Pharmaceutical Schedule for hospital use with presentations ranging from 1.25 mg per ml to 5 mg per ml, but is not currently listed in Section B for community use and is not readily used or accessible in hospice settings. The Subcommittee considered that bupivacaine is long-acting and therefore may not be appropriate for episodic symptoms.

4.10. The Subcommittee noted that lidocaine (lignocaine) gel 2% is currently listed on Section B of the Pharmaceutical Schedule, available as a tube and as a urethral syringe (US); both presentations are funded only if prescribed for urethral or cervical administration and the prescription is endorsed accordingly.

4.11. The Subcommittee considered that opioids are often ineffective in treating rectal pain/tenesmus and that their use is generally avoided if possible. The Subcommittee noted that local or topical anaesthetics have few systemic side effects but may provide benefit only in some people. Members considered that glyceryl trinitrate, which is funded for treatment of chronic anal fissures in the community (Section B) and is listed in for hospital use (Section H) without restriction, may provide benefit for some patients when used in combination with other medicines.

4.12. The Subcommittee considered that patients with intractable rectal pain/tenesmus have an unmet health need due to limitations of the currently funded pharmaceuticals and considered that having another treatment option available to treat intractable rectal pain/tenesmus and therefore delay or prevent hospice care would be desirable.

4.13. The Subcommittee noted that use of lidocaine gel 2%, urethral syringe in New Zealand has increased over recent years and considered this is unlikely to be due to an increase in catheterisations (see also part 7.20 of this record). The Subcommittee noted that there are anecdotal reports of it being used in New Zealand for other indications including localised neuropathic pain, malignant wound or ulcer pain, postherpetic neuralgia in elderly patients experiencing side effects from oral or systemic agents, and occasionally for severe migraine, applied nasally at Accident & Emergency clinics. The Subcommittee considered that, while some use in other indications may be appropriate and beneficial in specific cases despite limited evidence (if any) for such use, this use would be outside of the current funding restrictions.

4.14. The Subcommittee noted that there is limited evidence for treatment of rectal pain/tenesmus in palliative care in general and noted that the applicants have not provided any evidence in support of the use of rectal administration of lidocaine specifically. The Subcommittee considered that in the palliative care setting evidence is often limited to anecdotal case reports.

4.15. The Subcommittee noted a systematic review of the literature for efficacy of interventions for the palliative treatment of rectal tenesmus in patients with cancer, which identified 9 case series investigating pharmacological (bupivacaine, diltiazem, lidocaine, methadone, mexiletine hydrochloride and nifedipine), anaesthetic and endoscopic laser

interventions (Laoire AN et al. Palliative Medicine 2017;31:975-81). The authors noted that heterogeneity of the case series prevented meta-analysis and concluded that there is a significant gap in research of palliative care for rectal tenesmus.

4.16. The Subcommittee noted a single patient case report in support of the rectal administration of bupivacaine hydrochloride solution 0.05% - 0.1%, in which the patient achieved significant pain relief within 10 to 15 minutes post dose, with a duration of analgesia for 4.5 to 11 hours, and without any reported systemic effects (Zaporowska-Stachowiak I et al. OncoTargets Ther 2014;7:1541-50). The authors concluded that bupivacaine administered rectally was a valuable option for palliative treatment of rectal pain/tenesmus due to cancer. The Subcommittee noted that bupivacaine solution is not currently listed in Section H at the concentrations investigated.

4.17. The Subcommittee considered that there are anecdotal reports of topical lidocaine gel 2%, urethral syringe used in combination with morphine to provide a successful treatment with one syringe per episode, and expert opinion reports stating that lidocaine is sometimes a beneficial therapy.

4.18. The Subcommittee considered that the evidence base for palliative treatment of rectal pain/tenesmus is poor, noting that it is based on anecdotal reports, case reports, case series and expert opinion. The Subcommittee noted that evidence from palliative care settings is known to be limited and can be affected by variation between treating centres.

4.19. The Subcommittee considered that lidocaine gel 2%, urethral syringe could be more appropriate for treatment of intractable episodic rectal pain/tenesmus than other treatments such as rectal administration of bupivacaine solution; noting that bupivacaine is longer acting, is not available for use in community or hospice settings, and is not funded at the investigated concentrations.

4.20. The Subcommittee considered that successful use of lidocaine gel 2%, urethral syringe for patients with rectal pain could delay or prevent hospice admissions and provide savings, noting the relatively low cost per dose of lidocaine compared to the cost of hospice care for pain relief.

4.21. The Subcommittee considered that the applicants' estimate that roughly 60 to 65 people would be suitable to receive lidocaine gel 2%, urethral syringe annually for intractable rectal pain was reasonable, noting the applicants proposed dosing up to three times daily for two to three months. The Subcommittee considered that the likely use would be one to two syringes per day, up to a maximum of six per day in some cases per patient. The Subcommittee considered that the use of lidocaine in this setting would likely be in combination with other treatment options.

4.22. The Subcommittee considered that if the restriction by endorsement was widened to include rectal administration in the palliative care setting, then there would likely be use beyond intractable rectal tenesmus, for example in indications such as ulcer or wound pain. The Subcommittee considered that funding lidocaine gel 2%, urethral syringe with Special Authority criteria, rather than funding with a restriction by endorsement, would help to limit its use to the intended patient population. The Subcommittee considered some private use (purchased privately) would also be likely to continue.

4.23. The Subcommittee considered that, due to the noted absence of evidence for interventions in palliative care, and the anecdotal reports of usage of lidocaine gel 2% urethral syringe outside of the funded indications, it would be useful for the Analgesics Subcommittee to review a PHARMAC-prepared paper on topical analgesia in palliative care in future. The Subcommittee considered that PHARMAC may like to further

investigate the increasing use of lidocaine gel 2%, urethral syringe in other indications such as use for malignant wounds or ulcers, including estimates of patient numbers.

5. Doxylamine for nausea and vomiting associated with pregnancy

Application

5.1. The Subcommittee reviewed two applications; one for doxylamine alone and the other for doxylamine in combination with pyridoxine, both for the treatment of nausea or vomiting of pregnancy.

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

Recommendation

5.3. The Subcommittee **recommended** that the application for doxylamine for the treatment of nausea or vomiting of pregnancy be declined. The Subcommittee made this recommendation within the context of anti nausea treatments based on the current health need of this patient group (noting the availability of funded alternative treatments), the poor evidence of benefit from doxylamine (noting the lack of comparative evidence against other antiemetics), the likely high cost of this medicine compared to funded alternatives, and the lack of a registered product for safe use in pregnancy.

5.4. The Subcommittee **recommended** that PHARMAC provide a copy of the record for this item to the Reproductive and Sexual Health Subcommittee for their information.

Discussion

5.5. The Subcommittee considered that most nausea or vomiting of pregnancy is mild, however, it can be severe in up to 30% of cases and that it can impact on family and whānau. The Subcommittee noted that it can also be potentially life-threatening to the mother and foetus (e.g. hyperemesis gravidarum which affects fewer than 2% of pregnant women). The Subcommittee noted that there is evidence that Pacific people experience higher rates of hyperemesis gravidarum itself and higher rates of hospitalisation due to hyperemesis gravidarum (Jordan et al. NZMJ 1995;108:342-4, Sapoaga et al. J Primary Health Care 2010;2:105-10).

5.6. The Subcommittee noted that PHARMAC estimate 74,200 people may have nausea or vomiting of pregnancy in New Zealand each year, and that of these 7,400 likely seek pharmaceutical treatment. The Subcommittee considered that in general people who are pregnant may be more risk averse when considering medications than people who are not pregnant.

5.7. The Subcommittee noted that there are a range of currently funded pharmaceuticals that may be used in standard of care for nausea or vomiting of pregnancy, including metoclopramide, pyridoxine, chlorpromazine, cyclizine, promethazine and ondansetron. The Subcommittee considered that the health need of patients with nausea or vomiting of pregnancy can be met by the currently available treatment options.

5.8. The Subcommittee noted that doxylamine is a first-generation antihistamine and that there are a range of doxylamine combination products and tablets available internationally and over the counter in New Zealand (eg for the treatment of cold and 'flu symptoms). The Subcommittee noted that the only single agent doxylamine product approved in New Zealand is indicated for temporary use for insomnia and is available

as 25 mg gel capsules that cannot be divided. The Subcommittee noted that the American College of Obstetricians and Gynecologists (ACOG) has proposed several doxylamine dosing regimens ranging from 30 mg to 40 mg per day (12.5 mg three to four times per day, or 10 mg in the morning, 10 mg mid-afternoon and 20 mg at bedtime, or 20 mg in the morning and 20 mg at bedtime) for the treatment of nausea or vomiting of pregnancy. The Subcommittee considered that 25 mg gel capsules would be unsuitable for use in nausea and vomiting of pregnancy where dose adjustment and division may be needed.

5.9. The Subcommittee noted that there is no Medsafe-approved doxylamine product that is registered for the treatment of nausea or vomiting of pregnancy, and that there is no single-agent doxylamine product registered for this indication in any country. The Subcommittee noted that registered products undergo Medsafe's assessment of efficacy and safety, and the Subcommittee considered that certainty of a product's quality, safety and risk of teratogenic effects (abnormalities due to foetal exposure) is important for potential use in pregnancy.

5.10. The Subcommittee noted that doxylamine has been proposed by the applicants to be used either as a first-line treatment in combination with pyridoxine, or as a second-line treatment following failure of conservative treatment.

5.11. The Subcommittee noted that the applicants' rationale for doxylamine use in pregnancy is that it is considered safe compared to other products and noted that doxylamine is approved by the FDA for this indication (Diclegis combination product [doxylamine 10 mg, pyridoxine 10 mg, delayed-release tablet] indicated for nausea and vomiting of pregnancy in women who do not respond to conservative management (Diclegis Highlights of Prescribing Information. FDA, 2013).

5.12. The Subcommittee noted the results of a double-blind, randomised, active-controlled trial of ondansetron (4 mg) plus placebo compared to the combination of doxylamine 12.5 mg-pyridoxine 25 mg for five days in 36 adult women with nausea and vomiting of pregnancy who were at less than 16 weeks gestation and had received no previous treatment with antiemetics (Oliviewa et al. Obstet Gynecol 2014;124:735-42).

5.13. The Subcommittee noted that Oliviewa et al. used a 100 mm visual analogue scale (VAS) to assess the primary outcome, improvement in nausea, and reported a significant improvement with ondansetron compared to doxylamine and pyridoxine (median VAS score decreased 51 mm [interquartile range, IQR, 37 to 64] compared with 20 mm [IQR 8 to 51]; *P*=0.019). There was a significant reduction in vomiting with ondansetron, also assessed using the VAS (median VAS decreased 41 [IQR 17 to 57] compared with 17 [-4 to 38]; *P*=0.049). There were no significant differences in the rate of adverse events between the two treatment groups.

5.14. The Subcommittee noted the results of a double-blind, randomised, placebo-controlled trial that evaluate the effectiveness of doxylamine succinate 10 mg-pyridoxine hydrochloride 10 mg delayed-release preparation, administered as two tablets daily) compared with placebo for 14 days in 256 adult women with nausea and vomiting of pregnancy who were between seven to 14 weeks pregnant and had not responded to conservative management with dietary and lifestyle advice (Koren et al. Am J Obstet Gynecol 2010;203:571.e1-7). The Committee noted that study drug dose increases up to four tablets daily could be made according to patient's symptoms.

5.15. The Subcommittee noted that Koren et al. reported a significantly larger improvement from baseline in symptoms of nausea and vomiting of pregnancy with doxylamine-pyridoxine compared with placebo based on both the pregnancy unique quantification

of emesis score (-4.8 Diclectin vs -3.9 placebo; *P*=0.006) and quality of life (mean difference in global assessment of well-being; 2.8 doxylamine-pyridoxine vs 1.8 placebo; *P*=0.005). There were no significant differences in the rate of adverse events between the two treatment groups. The Subcommittee considered the improvement of 0.9 on a scale of 0 to 15 was unlikely to correspond to clinical benefit.

5.16. The Subcommittee also noted the following publications regarding doxylamine (and pyridoxine) in the treatment of nausea or vomiting of pregnancy:

- Fejzo et al. Nat Rev Dis Primers 2019;5:62
- ACOG Committee on Obstetric Bulletins. Obstet Gynecol 2018;131(1):e15-e30
- O'Donnell et al. Health Technol Assess 2016;20(74)
- Slaughter et al. NEJM 2014;370:1081-3
- Tan et al. Australian Family Physician 2016;45:564-568
- Chen RC. The management of nausea and vomiting in pregnancy [unpublished case history and review of antiemetic agents with special attention to pyridoxine-doxylamine]. Auckland, NZ; provided with funding application, 2019 August.
- Matthews et al. Cochrane Database Syst Rev 2015;9:CD007575

5.17. The Subcommittee noted that the evidence base for doxylamine in the treatment of nausea or vomiting of pregnancy consists of two randomised, controlled, clinical trials and assorted other evidence such as case studies and guidelines. The Subcommittee considered that the guidelines were based on variable, low-quality evidence, and noted that the authors of the Cochrane review of interventions for nausea and vomiting in early pregnancy stated that there was insufficient evidence to support any particular intervention.

5.18. The Subcommittee noted that there was insufficient information about the risk of teratogenic effects from doxylamine use in pregnancy. The Subcommittee noted that the current clinical practice guidelines and pathways in New Zealand lead to use of ondansetron for patients with severe nausea or vomiting of pregnancy that is not responsive to other treatments, and considered that based on recent meta-analyses, ondansetron is not known to cause teratogenic effects.

5.19. The Subcommittee considered there is variation between prescribers and DHBs and noted that, contrary to the New Zealand practice guidelines, survey results from one applicant indicate that ondansetron is one of several agents used for first-line treatment of nausea and vomiting of pregnancy. Members considered that ondansetron use in this setting is less than that of pyridoxine, metoclopramide, promethazine, cyclizine and prochlorperazine.

5.20. The Subcommittee considered that the clinical trial evidence did not provide sufficient comparative safety and efficacy data because the trials used comparators that may not be used for standard of care in New Zealand patients with nausea or vomiting of pregnancy (ondansetron as a first-line treatment, and placebo as a second-line treatment following failure of conservative treatment). The Subcommittee considered that overall, the evidence was poor and that there was no strong evidence to support a benefit of doxylamine compared to other funded treatment options in the treatment of

nausea or vomiting of pregnancy, and that there was no evidence of a greater benefit in any particular subgroup.

5.21. The Subcommittee noted that doxylamine (as a proprietary product in combination with pyridoxine hydrochloride) has been considered for funding in Scotland and Wales for the management of nausea and vomiting of pregnancy but was not recommended for funding by those agencies due to insufficient cost-effectiveness data. The Subcommittee noted that guidance on use of doxylamine/pyridoxine from the National Institute of Health and Care Excellence (NICE, UK) states that it is a more costly option for patients for whom conservative management is ineffective and that there is no evidence of how the safety and efficacy of doxylamine/pyridoxine compares to first-line treatment options (eg antihistamines and phenothiazines).

5.22. The Subcommittee noted that the applicant has proposed doxylamine would be used at a daily dose of 25 mg once daily; if used for 60 days, this would cost approximately $72 per pregnancy and would result in a gross cost of approximately $160,000 to the Pharmaceutical Budget for the treatment of 2,200 people per year. The Subcommittee noted that doxylamine has a variety of dosing regimens and considered that the applicant's estimated daily dose of 25 mg would be too low for modelling purposes, therefore the likely cost would be higher although the optimal dosing remains uncertain. The Subcommittee noted that even with costs offset by reduced use of funded alternatives, doxylamine costs significantly more per pregnancy than pyridoxine 50 mg three times daily (approximately $4.90), metoclopramide 10 mg three times daily (approximately $2.30) and for ondansetron 8 mg three times daily (approximately $17.20) for an equivalent time period.

5.23. The Subcommittee noted that PHARMAC estimate approximately 740 to 2,200 people would likely access doxylamine were it to be funded in New Zealand for this indication. The Subcommittee considered that the true proportion of severe cases in New Zealand would impact on the estimate of the total number of people seeking pharmaceutical treatment. The Subcommittee considered that the true number of patients likely to access doxylamine may be higher than PHARMAC had estimated if there was a clinical view that doxylamine was safer than other funded treatment options.

5.24. The Subcommittee considered that, if doxylamine were funded for nausea or vomiting of pregnancy, it would be used predominantly as a second-line or third-line treatment (with some first-line use) and that it would be used in combination with other pharmaceuticals, although it would replace some other antiemetics. The Subcommittee considered that PHARMAC could separately model first-line use and second-line use of doxylamine in any economic assessments undertaken.

5.25. The Subcommittee considered that treatment may continue for up to three months, rather than 60 days estimated by PHARMAC staff. The Subcommittee considered that the appropriate comparator for modelling purposes would be any of the other currently funded antiemetics that are commonly used for this indication in New Zealand (ie not placebo), or if considered for funding as cost-neutral to another agent then either metoclopramide or pyridoxine would be appropriate comparators.

5.26. The Subcommittee considered that there was no evidence that the use of doxylamine would prevent hospitalisations or presentation to emergency departments, compared to other funded antiemetics.

5.27. The Subcommittee considered that if doxylamine were to be funded without restriction, it is likely that prescribers would continue to use medicines that they are experienced with, although some would be strongly in favour of doxylamine. The Subcommittee

considered that additional use of doxylamine in patients with insomnia would be likely due to the withdrawal of doxepin and dothiepin.

6. Therapeutic Group and NPPA Review

Expenditure Summary

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

6.2. The Subcommittee considered expenditure on oxycodone products remained high, but considered that the trend towards reduced expenditure was encouraging in terms of responsible use of opioids.

6.3. The Subcommittee noted a trend of increasing expenditure in the anaesthetics therapeutic sub-group, and considered this was due to increasing use of lidocaine 2% gel.

Named Patient Pharmaceutical Assessment (NPPA)

6.4. The Subcommittee considered NPPA applications received since 1 March 2018 for pharmaceuticals in the Analgesics, Anaesthetics and Antinausea and Vertigo agents therapeutic subheadings.

6.5. The Subcommittee noted a number of NPPA applications had been received for cannabidiol and other cannabinoids. The Subcommittee noted that an application for the listing of cannabidiol with tetrahydrocannabinol (Sativex) had previously been assessed by PTAC at its August 2015 meeting and had been recommended for decline. The Subcommittee noted that no other schedule funding application has been received by PHARMAC for the funding of any other cannabidiol or cannabinoid product.

6.6. The Subcommittee considered that evidence for the use of cannabis and related products in the management of pain is emerging. The Subcommittee considered that cannabis use for pain management is occurring in the community, and that this indication for use is increasing in prevalence. The Subcommittee considered that it is likely that a funding application will be received by PHARMAC in the future cannabinoid type products and that the Subcommittee would like to consider the evidence at that time.

6.7. The Subcommittee noted a number of applications had been received for ketamine for use in the palliative care setting. The Subcommittee noted there was some geographic variation in the origin of these applications. The Subcommittee considered this was likely due to limited evidence for its use and variations in expert opinion. The Subcommittee considered that some hospices may be funding the use of ketamine via private means outside of the Combined Pharmaceutical Budget (CPB) and that this may also be contributing to the geographic variation.

6.8. The Subcommittee considered that there exists a high unmet health need for the small number of patients in the end of life setting who have intractable pain that is not responsive to conventional treatments. The Subcommittee considered that the unmet need is further confounded by national variability in access to interventional procedures for management of end of life pain. The Subcommittee noted that access to ketamine is available for patients in DHB hospitals and considered that there may be limited evidence for its use in the non-palliative care setting. The Subcommittee considered that funded access to ketamine should be made available for patients in the palliative care setting as well.

6.9. The Subcommittee noted that PTAC had previously considered ketamine for intractable pain in the palliative care setting and had recommended it for decline at its meeting in August 2011. The Subcommittee noted that PTAC had reaffirmed the decline recommendation at its meeting in November 2012 following the publication of Hardy et al. J Clin Oncol. 2012;30:3611-7 regarding burst ketamine therapy. The Subcommittee noted that PTAC had expressed comfort with the arrangement that patients requiring treatment with ketamine infusions go via the NPPA process. The Subcommittee considered that access to ketamine via Special Authority would be a more suitable pathway than via NPPA, and would likely improve equity of access. The Subcommittee considered that in many cases a patient would be deceased prior to a NPPA application being processed.

6.10. The Subcommittee considered that additional evidence investigating the use of ketamine in intractable pain in palliative care was unlikely to be generated.

6.11. The Subcommittee **recommended** that ketamine be funded via Special Authority for the treatment of intractable pain for patients in the end of life setting, based on unmet health need and the suitability benefit regarding the timing of approval of funding in comparison to funding via NPPA.

6.12. The Subcommittee considered that the number of patients accessing ketamine treatment was likely to be small; around 75 patients per year. The Subcommittee considered that in total patients would receive treatment for a maximum duration of one week, at an average dose of 0.1 mg/kg/hour, for an average total lifetime dose of 250 mg per patient. The Subcommittee considered that between 1/3 to 1/2 patients would stop treatment prematurely due to adverse events.

6.13. The Subcommittee considered that Special Authority criteria could be developed that would include the management of intractable pain in the end of life setting. The Subcommittee considered that Special Authority criteria could be developed such that use would be limited to people in the hospital, hospice or in the community setting under the care of a palliative care service.

Horizon scanning

Alvimopan

6.14. The Subcommittee noted that alvimopan is an opioid antagonist that can reduce the constipating effects of opioids without affecting the analgesic effects as it has a limited ability to cross the blood-brain barrier. The Subcommittee noted that this medicine has not been submitted to Medsafe for approval. The Subcommittee considered that any unmet need for this medicine had likely been met by the funding of methylnaltrexone (which was listed in the Schedule from 1 January 2018). The Subcommittee considered that methylnaltrexone and alvimopan could be considered as part of one class of medicines.

Monoclonal antibodies for migraine (i.e. erenumab, framenezumab and galcanezumab)

6.15. The Subcommittee noted that a number of monoclonal antibodies were in development or available internationally for the treatment of migraine. The Subcommittee noted that erenumab and galcanezumab had been submitted to Medsafe for approval. The Subcommittee noted that no funding applications had been received for any of these agents to date.

6.16. The Subcommittee considered that patients in New Zealand are aware of these medicines being available in international markets, including in Australia, and have begun asking about their clinicians about access to these.

6.17. The Subcommittee considered that the funded alternatives for intractable migraine were dihydroergotamine infusions, administered over 5 days in the out-patient setting, and lidocaine infusions, administered over 10 days in the in-patient setting. The Subcommittee considered that in some patients clostridium botulinum toxin type A injection was an effective funded alternative, but that this was not effective in all individuals. The Subcommittee considered that there exists an unmet need for effective treatments in intractable migraine based on the suitability and health resource usage requirements of existing funded alternatives.

Lidocaine 5% patches

6.18. The Subcommittee noted that lidocaine 5% patches are approved in other jurisdictions but have not been submitted to or approved by Medsafe. The Subcommittee considered that there may be a place for this pharmaceutical in the management of post-herpetic neuralgia in the context of funded topical anaesthetics (see also section 5.24 of this document).

Anaesthetics

Lidocaine 2% gel, urethral syringe

6.19. The Subcommittee noted recent usage and expenditure data for lidocaine 2% gel, urethral syringe in the community and hospital settings. The Subcommittee considered that usage has continued to increase over time in both settings. The Subcommittee considered it was likely that this pharmaceutical was being routinely used outside of the funded indications rather than this reflecting an increased number of catheterisations.

6.20. The Subcommittee noted a recent brand change for lidocaine 2% gel, urethral syringe, and noted that PHARMAC had received correspondence from three DHBs since awarding sole supply that indicated concerns regarding the suitability and safety of the funded brand.

6.21. The Subcommittee noted that PHARMAC has reviewed its approach to consultation on the annual tender list as a result of this feedback. The Subcommittee noted that the brand would be changing again as a result of a request from the supplier. The Subcommittee considered that, for any future brand changes to this pharmaceutical, the following groups should be consulted; urologists and urology nurses, Urological Society of Australia and New Zealand (USANZ), primary care practitioners, Royal New Zealand College of General Practitioners (RNZCGP), nurses, Royal New Zealand College of Urgent Care (RNZCUC).

Propofol injection

6.22. The Subcommittee noted that from 1 December 2019 the Fresofol 1% MCT/LCT brand of propofol 10 mg per ml, 20 ml injection had been awarded Hospital Supply Status (with a discretionary variance limit of 10%) until 30 June 2022.

6.23. The Subcommittee noted that the Fresofol brand of propofol is presented in a glass ampoule, rather than in a vial. The previous incumbent brand was a vial presentation, and the 50 ml and 100 ml listed presentations are also vials. The Subcommittee noted that the supplier of Fresofol (Fresenius Kabi) has reported an increased demand for the 50 ml vial since the 20 ml glass ampoule was listed in the Schedule. The Subcommittee

considered there may be a preference for a vial formulation of propofol, as the formulation being an emulsion means any glass fragments cannot be seen through visual inspection and therefore needs to be filtered. The Subcommittee considered that because of the emulsion formulation it can be difficult to draw through a filter needle.

6.24. The Subcommittee considered that the 20 ml propofol ampoule would primarily be used as an induction agent when a patient is undergoing anaesthesia with volatile anaesthetic gases.

6.25. The Subcommittee considered that due to an increasing trend in anaesthetic practice to use total intravenous anaesthesia (TIVA) in place of volatile anaesthetic gases, that this may also contribute to an increase in demand for the 50 ml ampoule.

6.26. The Subcommittee considered that the growing preference for TIVA rather than anaesthesia using volatile anaesthetic gases could be contributing to an increase in demand for propofol and other intravenous anaesthetic agents in general. The Subcommittee considered that PHARMAC should express a preference for a vial presentation of propofol in future tender rounds.

Prilocaine 2% injection

6.27. The Subcommittee noted that PHARMAC had received correspondence indicating some anaesthetists are using prilocaine hydrochloride 2% hyperbaric (i.e. “heavy) injection, for spinal anaesthesia in ambulatory surgery.

6.28. The Subcommittee noted that prilocaine hydrochloride 2% injection is currently listed in Part II of Section H of the Schedule as “any brand”. The Subcommittee considered there are funded alternatives, for example lidocaine injection or bupivacaine injection, to prilocaine hydrochloride 2% plain injection. The Subcommittee considered that prilocaine 2% hyperbaric may be more suitable in comparison to standard prilocaine 2% due to it being able to be targeted to specific sites, resulting in the potential for a lower dose to be used, with a lower risk of adverse events and a more rapid recovery time. The Subcommittee considered that a rapid recovery time would be associated with more efficient use of other health resources.

Low-dose bupivacaine

6.29. The Subcommittee noted that a DHB had requested the listing in Section H of low dose bupivacaine or ropivacaine for use, predominantly in the obstetrics setting, to reduce the associated motor blockade induced with higher concentration anaesthetics.

6.30. The Subcommittee considered that in some hospitals the lower concentrations solutions would be made up by the pharmacy department. The Subcommittee considered that it may be appropriate to list a low concentration anaesthetic if it were cost neutral to the higher concentration alternatives. The Subcommittee considered that if the option was bupivacaine or ropivacaine then the preference would be for ropivacaine on the basis that it may have less potential for cardiotoxicity.

6.31. The Subcommittee considered that PHARMAC could engage with a national obstetrics group to establish whether there was an unmet clinical need for low dose ropivacaine.

Opioid analgesics

The use, misuse and harm of potent opioids in New Zealand

6.32. The Subcommittee noted that the Health Quality and Safety Commission (HQSC) is actively monitoring opioid usage in New Zealand as part of the Atlas of Healthcare Variation. The Subcommittee noted that the Ministry of Health is the authority responsible for the regulation of controlled drugs in New Zealand.

6.33. The Subcommittee reviewed the trends in usage and expenditure for opioid analgesics over the past five years in New Zealand.

6.34. The Subcommittee considered that in general, usage appeared to be stabilising and, in some cases, declining and that trends appeared to be inconsistent with international data where there had been an exponential increase in usage in recent years. The Subcommittee considered the data to be reassuring in relation to the use and misuse of opioids in New Zealand. The Subcommittee considered that it could review usage trends in future, and that it would be useful to split the usage data by geographical region and by diagnosis (i.e. for malignant or non-malignant pain). The Subcommittee considered that PHARMAC staff could write to the HQSC to request usage data that was split by indication if these data were not readily available to PHARMAC.

6.35. The Subcommittee noted a trend of increasing usage of fentanyl injection 2 ml ampoules. The Subcommittee considered that this may be due to an increasing trend of intranasal fentanyl being prescribed for incident pain in the oncology and palliative care settings. The Subcommittee considered the usage should continue to be monitored.

6.36. The Subcommittee noted that while overall usage of fentanyl patches is declining, there was a trend of increasing numbers of people aged 80 years and over being dispensed lower-dose fentanyl patches. Some Members considered that buprenorphine patches could be a suitable alternative for these patients.

6.37. The Subcommittee **recommended** that it was the appropriate group to provide PHARMAC with clinical advice regarding opioid usage trends, and that this should remain as a standing agenda item for its meetings. The Subcommittee **recommended** that it could highlight any concerns regarding opioid usage trends to PTAC should they arise.

Non-opioid analgesics (excluding NSAIDs)

Paracetamol oral liquid

6.38. The Subcommittee noted that the Medicines Adverse Reactions Committee (MARC) had reviewed a case of hepatic injury in a child who had received paracetamol at a dose in excess of the recommended dose.

6.39. The Subcommittee noted that paracetamol oral liquid 120 mg per 5 ml and paracetamol oral liquid 250 mg per 5 ml had been included in the 2019/20 invitation to tender and that a preference for the inclusion of a measuring device had been included.

6.40. The Subcommittee reviewed an open consultation by Medsafe on proposed changes to current warning and advisory statements for paracetamol. The Subcommittee considered that while it would be ideal to have only one concentration of paracetamol in order to reduce confusion, there remains a clinical need to maintain both concentrations. The 250 mg per 5 ml concentration would be most appropriate for the majority of paediatric patients, whereas the 120 mg per 5 ml concentration is required for neonates and infants.

Antinausea and vertigo agents

Aprepitant

6.41. The Subcommittee noted a trend of increased use of aprepitant. The Subcommittee recommended PHARMAC staff seek the advice of the Cancer Therapeutics Subcommittee of PTAC (CaTSoP) regarding whether this trend was clinically appropriate.

6.42. The Subcommittee noted that alternative NK-1 antagonists may be available in future. The Subcommittee considered that it may be possible to establish a class-effect for these agents. The Subcommittee considered that either a head to head comparative study or a network meta-analysis could be appropriate to establish this.

Ondansetron

6.43. The Subcommittee noted a trend of increasing use of ondansetron. The Subcommittee considered this may be related to clinical preference and recent reductions in price, but that there may be other anti-emetics that would be more appropriate. The Subcommittee **recommended** that PHARMAC consider engaging its responsible use of medicine providers to develop educational material regarding the appropriate use of antiemetics.

6.44. The Subcommittee noted that ondansetron had recently been made funded on a Practitioners Supply Order (PSO) and considered that at its next meeting it would like to see a paper providing information on usage of medications in the Analgesic, Anaesthetic and Antiemetic Therapeutic group that are available on a PSO, with a view to reviewing the appropriateness of the current list of medications available on PSO.