

**Analgesics Subcommittee of the Pharmacology and Therapeutics Advisory Committee  
(PTAC)**

**Meeting held on 27 March 2018**

**(minutes for web publishing)**

Analgesics Subcommittee minutes 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 Analgesics Subcommittee meeting; the relevant portions of the minutes relating to Analgesics Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Analgesics 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.

These Subcommittee minutes was reviewed by PTAC at its meeting on 9 & 10 August 2018, the record of which will be available in due course.

## **Record of the Analgesics Subcommittee meeting held at PHARMAC on 27 March 2018**

### **1 Record of previous minutes**

- 1.1 The Subcommittee noted and accepted the record of the previous meeting held on 1 March 2016.

### **2 Previous Recommendations/ Action Points**

- 2.1 The Subcommittee noted action points made at its previous meetings in March 2016, December 2014, and September 2013, and the current status of these action points.
- 2.2 The Subcommittee noted that pregabalin will be funded in both Section B and Section H of the Pharmaceutical Schedule from 1 May 2018 without restrictions. The Subcommittee considered that in addition to its registered indications, pregabalin would also potentially be used for the treatment of generalised anxiety disorder and insomnia.
- 2.3 The Subcommittee discussed the action point from its 2012 recommendation to list methoxyflurane with a high priority, and in Section B of the Pharmaceutical Schedule with a medium priority, for patients undergoing painful procedures with an expected duration of less than 1 hour. The Subcommittee noted that methoxyflurane was listed in Section H of the Pharmaceutical Schedule in 2013 for this indication, and that a proposal to fund methoxyflurane for community, pre-hospital use has received positive PTAC recommendation in 2016 and has been prioritised. The Subcommittee noted a protocol could be sought from St John for use in pre-hospital trauma settings. The Subcommittee noted expanding use for procedural pain, with a favourable safety profile versus IV sedation options such as ketamine plus midazolam, although the evidence in this setting remained limited.

### **3 Correspondence and Matters Arising**

#### ***Responsible use of opioids***

- 3.1 The Subcommittee noted increasing international and local concern around inappropriate long-term prescribing and abuse of prescription opioids for chronic non-malignant pain. They also noted the significant increase in prescription opioid-associated mortality in the US and Australia over recent years.
- 3.2 The Subcommittee noted the traditional acute pain model, where pharmacological interventions are prescribed appropriately to reduce acute pain, is often ineffective in the treatment of chronic non-malignant pain. The Subcommittee considered that treatment of chronic, non-cancer pain requires a biopsychosocial multidisciplinary team approach with regards to assessment and management. The Subcommittee considered that the evidence of benefit for the long-term use of strong opioid analgesics in the management of chronic non-cancer pain was limited and there was some evidence that use of opioids were not superior to non-opioids in the treatment of chronic non-cancer pain (Krebs et al, JAMA 2018;319(9):887-82). The Subcommittee considered that there are a number of significant risks and adverse effects associated with the use of opioids in the chronic non-malignant pain setting.

- 3.3 The Subcommittee noted US data published by the Centers for Disease Control and Prevention (CDC, <https://www.cdc.gov/drugoverdose/data/overdose.html>) on prescription opioid overdose and deaths, and noted that opioids were involved in approximately 42,000 deaths in the US in 2016. The Subcommittee noted that approximately 40% of all opioid overdose deaths involved a prescription opioid. The Subcommittee noted that opioid overdose deaths were five times higher in 2016 than in 1999, and that the age group of people where were most likely to die of an overdose were aged between 25 to 54 years. The Subcommittee noted that the Center for Disease Control and Prevention in the USA have recognised opioid abuse as an epidemic.
- 3.4 The Subcommittee noted Australian data published by the Royal Australian College of General Practitioners (Monheit et al, AFP 2016, Vol 45, 862-6) which reported an increase in the use of prescription pharmaceuticals for non-medical purposes, and that the number of people in needle and syringe programs who reported that the last drug injected being an opioid increased from 7% in 2000 to 23% in 2015. The Subcommittee noted that of all overdose deaths (from pharmaceuticals, illegal drugs, and alcohol) in the state of Victoria, pharmaceuticals had a role in around 80% of deaths each year. The Subcommittee noted that benzodiazepines were the most frequent contributing drug group, accounting for 51.3% of all overdose deaths during 2009 – 2015, and that opioid analgesics contributed to an annual average of 48.5% of deaths during that time. The Subcommittee noted that the most common opioids causing death in the state of Victoria were oxycodone, codeine, and methadone.
- 3.5 The Subcommittee noted that in New Zealand all orally administered opioid analgesics are currently listed without restrictions or Special Authority. The Subcommittee noted that for those medicines considered to be higher risk, there are separate requirements in the Misuse of Drugs Regulations that restrict the maximum supply for those medicines, as well as how these medicines must be prescribed (i.e, up to a maximum of 30 days supply per prescription, on a triplicate controlled drug prescription form). The Subcommittee noted that there was limited data available in New Zealand regarding prescription opioid abuse and mortality.
- 3.6 The Subcommittee noted a commentary by Ballantyne et al, 2015 (N Engl J Med 2015;373:2098-99) where the authors considered that the numerical pain intensity scale may not be the best measure of chronic pain control. The Subcommittee noted that 'suffering', which often affects people with chronic pain has multiple dimensions, of which pain is one. The authors considered that persistent helplessness and hopelessness in patients with chronic pain may be the root causes of suffering and may contribute to high levels of pain and disability. The Subcommittee noted the authors' view that the desire to maintain low pain scores in the management of chronic pain meant that there was a trade-off with other measures of health and wellbeing which would be adversely affected, such as worsened functioning, quality of life, and for some at-risk individuals, aberrant use of pharmaceuticals, addiction, and death.
- 3.7 The Subcommittee noted a New Zealand publication by Paul Morrow (NZMA, Feb 2018, Vol 131, No 1469) which highlights the extent of the opioid abuse problem in America, and cites a shift in the pattern of opioid abuse from natural and semisynthetic opioids, to synthetic opioids such as fentanyl and its analogues. The Subcommittee noted that opioid use more than doubled worldwide from 2001-03 to 2011-13, with Canada, Northern Europe, and Australia showing patterns similar to that of the US. The Subcommittee noted that the author indicates that there were 200 deaths reported in New Zealand attributed to

opioid or other psychedelic drug poisoning. The Subcommittee noted that a significant contributory factor to the rise in opioid addiction and dependence was the physician opioid prescribing practice for chronic non-cancer pain, leading to increased availability of prescription medication that may also be diverted to the illicit market.

- 3.8 The Subcommittee noted the general upward growth in strong opioid (morphine, oxycodone, tramadol, fentanyl patches) prescribing in New Zealand from the dispensing data, and considered that there was a disproportionate growth in opioid prescribing relative to what would be expected with population growth. The Subcommittee considered that the major contributor of growth in opioid prescribing was likely patients being prescribed opioids for the treatment of chronic, non-cancer pain. The Subcommittee noted that the demographics of the population who were being prescribed opioids in New Zealand were generally older, whereas in the US the patient demographic was much younger.
- 3.9 The Subcommittee discussed the increase in the number of people seeking access to addiction services, and considered that this increase was correlated with the increase in the number of people being prescribed opioids. The Subcommittee considered that approximately half of patients seeking help with addiction were those who became addicted after being prescribed opioid analgesics, whilst the other half probably reflect misuse of diverted prescription medications and other illicit drugs.
- 3.10 Members noted that there was limited access to multidisciplinary pain clinics in New Zealand, to manage patients with chronic pain. Members also noted that opioid analgesics were rarely initiated in multidisciplinary pain clinics.
- 3.11 The Subcommittee noted that initial opioid prescribing was generally appropriate for the relief of acute post-surgical pain, and considered that following the discharge of patients from hospital back into the community, prescribers in primary care may feel pressured to continue prescribing strong opioids. The Subcommittee commented that this patient population should be regularly reviewed by their GP if they continue to prescribe strong opioid analgesics and patients should be referred to multidisciplinary pain clinics or CADS (community alcohol and drug services) if functional deterioration or aberrant opioid use becomes problematic.
- 3.12 The Subcommittee considered that PHARMAC should carefully consider the potential consequences of abuse, misuse, and dependence in its funding assessments of new opioid medicines, as any new funding would likely increase the total opioid market and the number of patients being treated with a strong opioid.
- 3.13 The Subcommittee recommended that PHARMAC should engage education material providers and have an article written and disseminated to prescribers working in both community and hospital settings around the safe and appropriate prescribing of opioids, specifically highlighting the lack of evidence around the long-term use (any greater than three months) of strong opioid analgesics.
- 3.14 The Subcommittee recommended that PHARMAC collect prescribing and dispensing data for strong opioids and that these be made available, when required, to other government bodies. The Subcommittee considered that should there be signals of increasing prescription opioid dependence, abuse, or divergence, that PHARMAC could use restrictions on products such as fentanyl patches to ensure that opioids are targeted to those patients most likely to benefit and to minimise the risks of harm. The Subcommittee

noted this would be those with malignant pain or those who are under palliative care management.

### ***Buprenorphine patches***

- 3.15 The Subcommittee reviewed an application for buprenorphine patches for the treatment of severe chronic non-cancer pain. The Subcommittee note that this application was first received by PHARMAC in 2008, and reviewed by PTAC in 2009 where it was recommended for funding with a low priority. The Subcommittee noted that this application has been evaluated by PHARMAC and was prioritised in 2010. The Subcommittee noted that the reason buprenorphine patches remained unfunded was because of its relative low cost effectiveness compared to other investment options.
- 3.16 The Subcommittee noted that PHARMAC had recently received a revised commercial proposal that would increase its cost effectiveness.
- 3.17 The Subcommittee noted that since 2010, there have been a number of new opioid and non-opioid analgesic medicines funded and as a result, an increased number of pharmacological treatment options for pain management. The Subcommittee considered that buprenorphine patches were a relatively weak opioid, with controlled-release tramadol likely to be its nearest comparator.
- 3.18 The Subcommittee noted the trend of increased opioid prescribing in recent years, including fentanyl patches, and considered that buprenorphine patches would very likely increase the number of patients being exposed to opioids. The Subcommittee did not consider there was an unmet clinical need for an alternative transdermal option, and there was not a significant suitability advantage over other currently availability options.
- 3.19 The Subcommittee considered that the definition of severe chronic non-cancer pain is broad, and the overall treatment duration for this type of pain is likely to be long.
- 3.20 The Subcommittee noted that there is limited evidence of benefit and functional improvements for the use of opioids in the management of chronic pain. The Subcommittee noted conversely that there is extensive evidence to suggest possible harms resulting from long term opioid use. The Subcommittee considered that non-pharmacological therapy and non-opioid pharmacological therapy are the preferred treatment options for chronic pain to improve functional status and quality of life. The Subcommittee considered that there is unlikely to be a place in therapy for buprenorphine patches for the treatment of chronic non-cancer pain which is where this product is positioned.
- 3.21 The Subcommittee considered that buprenorphine has a moderate abuse potential, although this is somewhat attenuated by the patch formulation. The Subcommittee considered that should buprenorphine patches be funded, there would likely be a proportion of use that would be inappropriate and may be diverted, potentially causing societal harm.
- 3.22 The Subcommittee **recommended** that the application for buprenorphine patches for the treatment of severe chronic non-cancer pain be **declined**.

### ***Widening access to ketamine injections for emergency use***

- 3.23 The Subcommittee noted a clinician application requesting widening access to ketamine injections for emergency use in the pre-hospital setting for the management of acute trauma pain.
- 3.24 The Subcommittee noted that ketamine is a rapidly acting, anaesthetic agent causing dissociative anaesthesia. The Subcommittee noted that ketamine achieves pain relief comparable to morphine, with fewer risks of respiratory depression and vomiting, but higher risks of neuropsychological adverse events, such as hallucinations, nightmares, and dizziness. The Subcommittee noted that ketamine has been used extensively in emergency acute care by a range of first-response healthcare professionals. The Subcommittee noted that ketamine may avoid the use of morphine combined with benzodiazepines, which would be advantageous due to the lower risk of excessive sedation and respiratory depression.
- 3.25 The Subcommittee noted that a number of first response emergency personnel currently have access to ketamine for use in emergency settings. The Subcommittee noted the PRIME (Primary Response in Medical Emergencies) steering group report 2017 which lists the administration of ketamine (in all routes of administration) as within the scope of practice for intensive care paramedics. The Subcommittee further noted the St John's Clinical Procedures and Guidelines 2016-2018 which contain sets of circumstances under which ketamine could be administered, and by whom. The Subcommittee noted that medicines used in ambulances were funded from a separate funding stream outside of the Pharmaceutical Schedule. The Subcommittee considered that rural GPs who arrive at the scene of an emergency before an ambulance should also have access to ketamine for the treatment of acute trauma pain.
- 3.26 The Subcommittee noted that ketamine is currently funded only for use in hospitals, and noted the range of funded formulations and presentations available for ketamine. The Subcommittee considered that should ketamine be listed in the community schedule, that there would need to be stringent restrictions to ensure that it would only be used in the emergency setting, and not be prescribed to patients for the treatment of chronic pain. The Subcommittee considered that the pre-filled syringe formulation of ketamine would be the appropriate presentation of ketamine to be made available for use in the emergency setting.
- 3.27 The Subcommittee considered that the 'only on a PSO' restriction would be an adequate control to ensure that patients would not be prescribed ketamine inappropriately, and considered that this would give doctors the option to order ketamine to keep in their clinic or doctor's bag should they wish to. The Subcommittee considered that annual usage would likely be low (around 300 units, approx. 70 PRIME sites using <5 ampoules per year), and noted that PHARMAC would have the option to audit practices should usage be higher than expected. The Subcommittee noted that as with other controlled drugs that are currently being used and/or stored in the primary care setting, handling and storage of ketamine would need to comply with the relevant clauses in the Misuse of Drugs Act and Regulations.
- 3.28 The Subcommittee considered the clinical settings that ketamine syringes would be used in, the high acute health need of patients in traumatic situations, and the history of use that ketamine has in the emergency pre-hospital setting. The Subcommittee **recommended** that access to ketamine pre-filled syringes be widened to Section B of the Pharmaceutical Schedule available only on a PSO, limited to 2 syringes, with a **high priority**.

## 4 Therapeutic Group Review

### *Expenditure summary*

- 4.1 The Subcommittee noted the top expenditure items in the Analgesics, Anaesthetics, and Antinausea and Vertigo agents group. The Subcommittee noted that codeine-containing products (either in isolation or in combination with paracetamol) comprised a significant proportion of the general expenditure in these portfolios.
- 4.2 The Subcommittee considered that codeine was a poor and unpredictable analgesic agent, and considered that a significant amount of codeine was perhaps being prescribed for the treatment of cough. The Subcommittee considered that PHARMAC staff should bring a paper to a future PTAC meeting to review the evidence and benefit of codeine containing products (either in isolation or in combination with paracetamol) relative to other currently funded alternatives, to determine the merits of continuing to fund codeine as an analgesic agent. The Subcommittee noted although the use is high, the amount of codeine in the tablet combination with paracetamol funded in New Zealand (paracetamol 500 mg with codeine phosphate 8 mg) was sub-therapeutic, and on clinical grounds it could be considered for discontinuation.

### *Anaesthetics*

- 4.3 The Subcommittee noted that the community expenditure for this group of medicines is trending upwards over time, despite relatively stable prescription volumes. The Subcommittee noted that the significant share of expenditure comes from lidocaine hydrochloride.

### *Opioid analgesics*

- 4.4 The Subcommittee noted that prescription volumes of opioid analgesics have been increasing slowly over time, however despite this, the total expenditure in this group has been decreasing over the last 5 years. The Subcommittee noted that the biggest expenditure items in the opioid analgesics group are codeine, tramadol, and paracetamol with codeine.
- 4.5 The Subcommittee noted the April 2017 announcement by the FDA where it advised that additional contraindications be added to codeine to prevent its use in the treatment of pain or coughs in children younger than 12, and tramadol for the treatment of pain in children younger than 12 years. The Subcommittee noted that the tramadol would also have a new contraindication added, warning against its use in children younger than 18 for the treatment of pain after surgery to remove tonsils and/or adenoids.
- 4.6 The Subcommittee noted that the New Zealand Medicines Adverse Reactions Committee (MARC) have also been aware of the FDA's review on the safety of tramadol use in children. The Subcommittee noted that MARC will be reviewing the FDA's decision at a future meeting.

### *Non-opioid analgesics*

- 4.7 The Subcommittee noted the steady increase in prescription volumes for non-opioid analgesics and noted that by far the most commonly prescribed, and highest overall expenditure item is paracetamol.
- 4.8 The Subcommittee noted that the majority of analgesics (opioid and non-opioid) are off patent with numerous registered generic versions available.

### *Antinausea and Vertigo Agents*

- 4.9 The Subcommittee noted the steady increase in overall prescription volumes for anti-nausea and anti-vertigo treatments, and noted the significant increase in ondansetron prescription volumes over the last 5 years. The Subcommittee noted that despite the apparent shift in the choice of anti-nausea treatment, expenditure has dropped over time, and that this was likely attributable to savings obtained from the annual tender. The Subcommittee noted that ondansetron was placed in the 2016/17 Invitation to Tender, and that further savings could be achieved in this area.

### *Antimigraine treatments*

- 4.10 The Subcommittee noted that prescription volumes and expenditure for antimigraine treatments have remained stable. The Subcommittee noted that there was a significant price reduction in these treatments about 5 years ago, which was likely attributable to tender savings.

### *Neuropathic pain treatments*

- 4.11 The Subcommittee noted the expenditure on medicines used to treat neuropathic pain. The Subcommittee noted that these medicines are predominately categorized under the Nervous Systems Therapeutic Group, and are mostly used for the treatment of seizures. The Subcommittee considered that as most of these medicines were open listed and can be prescribed for a range of different indications, that it was difficult to draw trends on how their use over time has changed for the treatment of pain.
- 4.12 The Subcommittee noted that gabapentin and pregabalin will be open listed in the Pharmaceutical Schedule without restrictions from 1 May 2018, and considered that usage on these products will likely be significantly higher than what is currently observed.
- 4.13 The Subcommittee noted that SSRI's and clonidine were not generally used for neuropathic pain and could be removed from future TG reviews for this Subcommittee.
- 4.14 Subcommittee noted that mexiletine was used for neuropathic pain in pregnancy but had poor efficacy with an NNT of around 15.

### *Muscle relaxants*

- 4.15 The Subcommittee noted that both prescription volumes and expenditure on muscle relaxants have been growing year on year, and that both volume and expenditure growth were likely driven by increased use of orphenadrine.



*Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*

- 4.16 The Subcommittee noted that prescription volumes have been increasing consistently year on year driven predominately by an increased use of ibuprofen (all formulations). The Subcommittee noted a sharp reduction in expenditure in recent years, which was likely from tender savings.

*Horizon scanning*

*Alvimopan*

- 4.17 The Subcommittee noted that alvimopan was an opioid antagonist that reduces the effects of opioids on the gastrointestinal tract but not the analgesic effect as it doesn't cross the blood brain barrier. The Subcommittee noted that alvimopan has not been submitted to Medsafe for registration.

*Ibuprofen with codeine*

- 4.18 The Subcommittee noted that there is a registered product currently available in New Zealand containing ibuprofen with codeine. The Subcommittee noted that PHARMAC has not received a funding application for this medicine. The Subcommittee also noted its previous consideration that all codeine-containing medicines should have their evidence reviewed by the Subcommittee and/or PTAC, to determine the merits of ongoing funding of codeine as an analgesic agent.

*Fentanyl nasal spray 4 mg per ml and 1 mg per ml*

- 4.19 The Subcommittee noted that there is a Medsafe registered product available, however no funding application has been received by PHARMAC for this product.

*Tapentadol*

- 4.20 The Subcommittee noted that there is currently no Medsafe registered product. The Subcommittee considered that tapentadol may be a safer and more suitable alternative to tramadol when used in paediatric patients due to the fact that tapentadol does not have any active metabolites. The Subcommittee noted that the supplier was considering registering tapentadol with Medsafe and expressed their interest in seeing a funding application for this product.

*Oxycodone with naloxone*

- 4.21 The Subcommittee noted that whilst there is a Medsafe registered product available, PHARMAC has not received a funding application for this product.

*Fentanyl degradable patches*

- 4.22 The Subcommittee noted that there is no Medsafe registered product.

*Fentanyl lollipops*

- 4.23 The Subcommittee noted that there is no Medsafe registered product.

*Lidocaine patches 5%*

4.24 The Subcommittee noted that there is no Medsafe registered product.

*Oxymorphone*

4.25 The Subcommittee noted that there is no Medsafe registered product.

*Sufentanyl/ sufentanil*

4.26 The Subcommittee noted that there is no Medsafe registered product.

*Morphine with oxycodone*

4.27 The Subcommittee noted that there is no Medsafe registered product.

## **5 Fentanyl citrate sublingual tablets**

### **Recommendation**

5.1 The Subcommittee **recommended** that the funding application for fentanyl sublingual tablets for the treatment of breakthrough cancer pain be **declined**.

### **Discussion**

5.2 The Subcommittee reviewed a funding application from a supplier to list fentanyl sublingual tablets in Section B and Section H of the Pharmaceutical Schedule for the treatment of breakthrough cancer pain (BTCP).

5.3 The Subcommittee noted that fentanyl is a potent  $\mu$ -opioid analgesic with rapid onset of analgesia and short duration of action. The Subcommittee noted that fentanyl has approximately 100-fold more potent than morphine as an analgesic, and that secondary effects of fentanyl on the central nervous system, respiratory, and gastro-intestinal function are typical of opioid analgesics and are considered to be class effects.

5.4 The Subcommittee noted that pain is a significant and frequent consequence of cancer and one of the most feared symptoms associated with the diagnosis of cancer. The Subcommittee noted that patients report that pain is associated with significant levels of physical discomfort, negative effects on their ability to engage in their usual activities, and diminished overall quality of life. The Subcommittee noted that breakthrough pain is a transitory pain that occurs despite the use of long-term, around-the-clock analgesia to control chronic pain. The Subcommittee noted that two types of breakthrough cancer pain (BTCP) exist: incident pain, which can be precipitated by predictable volitional factors (e.g. walking) or unpredictable non-volitional factors (e.g. coughing), and spontaneous pain that occurs unexpectedly.

5.5 The Subcommittee noted a recent meta-analysis by Van den Bueken-van Everdingen et al, 2016 (J Pain Symptom Manage 2016; 51(6):1070-90) where the authors reported pain prevalence rates of 39.3% after curative treatment; 55.0% during anticancer treatment; and 66.4% in advanced, metastatic, or terminal disease. The Subcommittee noted that authors reported moderate to severe pain (numerical rating scale score  $\geq 5$ ) in 38.0% of all patients.

- 5.6 The Subcommittee noted Davies et al 2013 (*J Pain Symptom Manage* 2013; 46(5):619-28) where the authors surveyed 1000 cancer patients in 13 European countries to characterise the nature and management of breakthrough pain. The Subcommittee noted that of the 1000 patients, 44% reported incident pain, 41.5% spontaneous pain, and 14.5% a combination. The Subcommittee noted that the median number of episodes was three a day, with the median time to peak pain intensity for spontaneous pain being 10 minutes, for patients with incident pain being five minutes. The Subcommittee noted that the median duration of untreated episodes were 60 minutes.
- 5.7 The Subcommittee noted that over 85% of surveyed patients stated that the pain stopped them doing something. The Subcommittee noted that patients with incident pain reported more interference with walking ability and normal work, whereas patients with spontaneous pain reported more interference with mood and sleep.
- 5.8 The Subcommittee noted that there are significant racial and ethnic differences in patients' ratings of BTCP severity, with non-Caucasian patients reporting more severe BTCP intensity compared with Caucasians. The Subcommittee noted that patients who were representative of racial or ethnic minority groups reported higher rates of pain-related disability, depression, and post-traumatic stress disorder, compared with Caucasian patients, as well as lower quality of life.
- 5.9 The Subcommittee noted that fentanyl is a highly lipophilic drug that is absorbed very rapidly through the oral mucosa and more slowly through the gastrointestinal tract. The Subcommittee noted that orally administered fentanyl undergoes pronounced hepatic and intestinal first pass effects.
- 5.10 The Subcommittee noted that ABSTRAL contains fentanyl formulated as a fast dissolving sublingual tablet. The Subcommittee noted that buccal absorption of fentanyl occurs over about 30 minutes, with the onset of pharmacological effect occurring within 10 minutes. The Subcommittee noted that ABSTRAL is designed to adhere to the mouth so that the active substance is absorbed directly into the systemic circulation, bypassing the gastrointestinal tract and the first pass effect in the liver.
- 5.11 The Subcommittee noted that ABSTRAL tablets are formulated in strengths ranging from 100 mcg to 800 mcg. The Subcommittee noted that the pharmacokinetics of ABSTRAL was shown to be dose proportional over the dose range of 100 to 800 mcg. The Subcommittee noted that the optimal dose of ABSTRAL for patients for the management of BTCP would be determined by upward titration, on an individual patient basis. The Subcommittee considered that during the dose titration phase, a number of different strengths of fentanyl sublingual tablets may be used. The initial dose of ABSTRAL used should be 100 micrograms, titrating upwards as necessary through the range of available dosage strengths.
- 5.12 The Subcommittee noted that a number of funded medicines with a rapid onset of action are currently available for the treatment of BTCP, such as oral immediate release morphine, oral immediate release oxycodone, subcutaneous fentanyl, compounded intranasal fentanyl sprays, and sublingual and buccal fentanyl using fentanyl injections. The Subcommittee noted that a number of these medicines are currently being used off-label.
- 5.13 The Subcommittee noted Velazquez et al. 2014 (*Adv Ther* 2014; 31(1):107-17), a prospective, longitudinal, double blind, randomised controlled study assessing the efficacy,

tolerability, and patient satisfaction of sublingual fentanyl (SLF) compared to oral morphine solution (OM) in the treatment of BTCP in patients whose pain was not managed on background treatment. The Subcommittee noted that a total of 40 patients were randomly assigned to one of the two groups, and that that mean pain intensity was consistently better in the SLF group than the OM group at all recorded time points ( $p=0.001$ ). The Subcommittee noted that whilst both groups had statistically significant difference in the mean pain intensity at 30 days with treatment compared with baseline, SLF had mean pain intensity levels lower than OM at all times when pain scores were measured (day 3, 7, 15, and 30).

- 5.14 The Subcommittee noted Zecca et al. 2017 (*J Clin Oncol* 2017; 35(7):759-65) a randomised, double blinded, double dummy, parallel-group trial to study whether 100µg fentanyl sublingual tablets (FSL) were non-inferior to 5mg subcutaneous morphine (SCM) in terms of its effect on pain intensity (PI) scores 10, 20, and 30 minutes after administration. The Subcommittee noted that the authors reported that the mean average pain scores at 10, 20, and 30 min (AVP\_30) was 5.0 and 4.5 for FST and SCM respectively, with a between group difference of -0.49 (95% CI -1.10 to 0.09). The Subcommittee noted that 30 minutes post treatment, a PI reduction of 33% was achieved in 71% of patients using both treatments, whereas a 50% reduction in PI was more frequent with SCM (57%) than FSL (52%).
- 5.15 The Subcommittee also noted the following single arm trials assessing the analgesic properties of sublingual fentanyl tablets:
- Uberall et al, *Curr Med Res Opin* 2011; 27(7):1385-94
  - Guitart et al, *Clin Drug Investig* 2013; 33:675-83
  - Guitart et al, *Clin Drug Investig* 2015; 35:815-22.
- 5.16 The Subcommittee considered that the trials demonstrated that fentanyl sublingual tablets having a rapid onset of action, however considered that the head to head trials were of low quality, had low participant numbers, and limited applicability to the New Zealand context. Furthermore, the Subcommittee felt that any benefits over the current standard of care were uncertain.
- 5.17 The Subcommittee noted the risks of divergence associated with other currently funded opioids. The Subcommittee considered that should fentanyl sublingual tablets be funded, the risk of divergence and abuse potential would be extreme. The Subcommittee noted the wide ranging strengths of fentanyl sublingual tablets available, and considered that should an opioid-naïve person be exposed to the higher strength tablets, that the risks of overdose and death would be high. The Subcommittee noted the increasing rates of abuse of fentanyl in the illicit market, and considered that should fentanyl sublingual tablets be listed, this would likely be a main source of supply for this market.
- 5.18 The Subcommittee noted the health need of patients with BTCP, the low quality evidence in support of fentanyl sublingual tablets, the availability of funded alternatives, and the significant risks of harm with divergence of fentanyl sublingual tablets. The Subcommittee considered that on balance, the risks of societal harm outweighs the benefits, and **recommended** that this application to fund fentanyl sublingual tablets for the treatment of

BTCP be **declined**. The Subcommittee considered that PHARMAC staff should forward a copy of this minutes to key palliative care groups within New Zealand for comment.

## **6      **Devices update****

6.1    The Subcommittee noted a presentation on PHARMAC's strategy for medical devices.