PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 25 March 2021

This meeting was held via videoconference, with the Chair and PHARMAC staff in attendance at PHARMAC office

The records of PTAC and Subcommittees of PTAC are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016. Note that this document is not necessarily a complete record of the meeting; only the relevant portions of the record relating to discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

PTAC and Subcommittees of PTAC may:

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

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

c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule

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

Present:

PTAC members:
Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Brian Anderson
Bruce King
Elizabeth Dennett
Giles Newton Howes
Jane Thomas
Jennifer Martin
Lisa Stamp
Matthew Strother
Sean Hanna
Stephen Munn
Tim Stokes

Apologies
Alan Fraser
Rhiannon Braund
Simon Wynn Thomas

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

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

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

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

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

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

2. Pneumococcal polysaccharide vaccine – Immunisation of people 65 years of age and over

Application

2.1. The Committee reviewed a supplier application for 23 valent pneumococcal polysaccharide vaccine for the immunisation of people 65 years of age and over.

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

Recommendation

2.3. The Committee **recommended** that pneumococcal polysaccharide vaccine (PPV23) for the immunisation of all people 65 years of age and over be declined.

2.4. In making this recommendation, the Committee considered that further advice is required from the Immunisation Subcommittee regarding:

2.4.1. The possible risks and benefits of funding the PPV23 for Māori; and additionally for Pacific people and others facing health disparities as a result of underlying disadvantage who are also under 65 years of age, and finally for those with comorbidities such as COPD or rheumatic heart disease;

2.4.2. The possible risks and benefits of funding the PPV23 for the general population under 65 years of age and whether there were any age groups that would potentially benefit most from immunisation with PPV23;

2.4.3. Whether repeat dosing would be required for an older patient population due to immunosenescence;

2.4.4. The relevance of herd immunity to pneumococcal infection;

2.4.5. The relevance of the current special groups listed in the Special Authority, and whether these should be revisited.

Discussion

2.5. The Committee noted an application from Merck, Sharpe and Dohme for pneumococcal 23 valent vaccine (PPV23) to be funded for all persons 65 to 80 years of age who have not received the PPV23 vaccination within the last 5 years and who were not older than 65 years of age at the time of prior vaccination.

2.6. The Committee noted that PPV23 is currently funded for children under 5 years of age, and all adults with: HIV infection, for patients post haematopoietic stem cell transplant or chemotherapy, pre- or post-splenectomy or with functional asplenia, pre- or post-solid organ transplant, renal dialysis, complement deficiency (acquired or inherited), cochlear implants, or primary immunodeficiency. The Committee noted that PHARMAC also funds one dose of pneumococcal conjugate vaccine (PCV13) for people with chronic conditions who are at higher risk of pneumococcal infection, with a maximum of three doses of PPV23 in a lifetime for revaccination of patients. The Committee noted that approximately 5,000 doses of PPV23 are administered in a year.

2.7. The Committee noted that it had previously reviewed applications for PPV23 in the requested population group (once in February 2014 and again in August 2015) and that both applications were recommended for decline. The Committee also noted that the proposal was reviewed by the Immunisation Subcommittee in February 2015, with no formal recommendation. The Committee noted that at the 2014 meeting, PTAC considered that the evidence of efficacy of PPV23 at a population level was poor, that the evidence for PPV23 in the elderly population was also poor, and that overall incidence of pneumococcal disease was falling. The Committee noted that in 2015, PTAC considered that there was high quality randomised controlled trial evidence of good effect against invasive pneumococcal disease (IPD) however, the strength of the randomised controlled trial evidence against either pneumococcal pneumonia or all-cause pneumonias in the general 65 years of age and over population was weak. PTAC considered that the supplier's cost-effectiveness model was not robust and could not be tested. The Committee noted that this subsequent resubmission contained new evidence and an updated cost-effectiveness model not previously considered by PTAC or the Immunisation Subcommittee.

2.8. The Committee noted that pneumococcal infection can lead to non-bacteraemic pneumococcal pneumonia (NBPP), which is responsible for up to 20% of community acquired pneumonia. The Committee noted that invasive pneumococcal disease (IPD) can present as meningitis or bacteraemia, and that 1 in 4 cases of IPD will suffer from bacteraemia. The Committee noted that IPD is a notifiable disease, and cases must be reported to the Institute of Environmental Science and Research (ESR), so data on incidence in New Zealand is robust. The Committee noted, however, that NBPP is not notifiable and accurate NZ data on incidence and prevalence is not available. The Committee also noted that the health needs of a person with pneumococcal infection are often greater in those with IPD and in those with comorbidities.

2.9. The Committee noted that rates of IPD for Māori and Pacific populations in New Zealand is 3.8 and 4.3 times higher than the rate for NZ Europeans, respectively. The Committee noted that of all IPD related mortalities in the Pacific population, 50% occur before the age of 50 years, and for Māori 50% of IPD mortalities occur by 54 years of age. The Committee noted that the IPD mortality rates for NZ Europeans is 50% by 65 years of age. The Committee also noted that Māori comprise approximately 16% of the population but contribute to 50% of total deaths from IPD by 64 years of age. The Committee considered that this demonstrates that the burden of disease from IPD is higher in a population younger than 65 years, and specifically in Māori and Pacific populations.

2.10. The Committee noted that in New Zealand the incidence of pneumococcal infection in those over 65 years of age has increased by 21% between 2016 and 2018, however, the incidence has increased 15% in the same time period for those 5-64 years of age. The Committee considered that more information should be sought from the Immunisation Subcommittee regarding any potential benefits if PPV23 were to be funded for a younger population, as well as its view on the age groups that would be the most appropriate to immunise with PPV23.

2.11. The Committee noted that PPVs stimulate a T-cell independent immune response, in contrast to PCVs, which stimulate T-cell memory response. The Committee noted that, theoretically, this means that PCV works better in children while PPV works better in adults, due to immunosenescence-related decrease in immune cell memory. The Committee noted that there are over 90 identified pneumococcal serotypes, and that PPV23 covers approximately 72% of the serotypes which are thought to cause disease in those over the age of 65 years in New Zealand, according to IPD data. The Committee noted there are also 15-valent and 20-valent PCVs in development.

2.12. The Committee noted 10 studies relating to the efficacy of PPV23 that have been published since previous PTAC and Subcommittee appraisals:

2.12.1. Kim et al. Vaccine. 2019;37:2797-804: a hospital based case-control study on the direct effectiveness of pneumococcal polysaccharide vaccine in elderly population. The Committee noted that the adjusted effectiveness against IPD and NBPP was not statistically significant, but when subgroup analysis was performed on the 65-74 age group, the adjusted PPV23 effectiveness was 57.4% against IPD (95% CI 19.4 to 77.5; p=0.009) and 35.0% for NBPP (95% CI 2.3 to 56.7; p=0.038).

2.12.2. Suzuki et al. Lancet Infect Dis. 2017;17:313-21: a prospective case-control study on the serotype-specific effectiveness of PPV23 against pneumococcal pneumonia in adults aged 65 years or older with community acquired pneumonia. The Committee noted that vaccine effectiveness for NBPP was 20.4% (95% CI 3.4% to 45.6%), and for PPV23 specific serotypes was 33.5% (95% CI 5.6% to 53.1%).

2.12.3. Falkenhorst et al. PLoS One. 2017;12:e0169368: a systematic review of vaccine efficacy in those aged 65 years and over (three randomised controlled trials, one pseudo-randomised trial, and 13 non-experimental observational trials were

included in the analysis). The Committee noted that vaccine efficacy against NBPP was 64% in the randomised controlled trials identified as having low bias, however, the Committee also noted that these trials were heavily weighted by a 2010 Japanese study (Maruyama et al. BMJ. 2010;340:c1004), with participants recruited from Japanese nursing homes. Additionally, the Committee noted that the meta-analysis reported for the two RCTs selected because of a lower risk of bias, had used the wrong denominators (patient-years rather than number of patients) in their calculations. This study was reviewed by the Immunisation Subcommittee in 2015, at which time the Subcommittee concluded that although the study reported that all causes of pneumonia and pneumococcal pneumonia were significantly higher in the placebo group than in the vaccine group, and that the death rate from pneumococcal pneumonia was also significantly higher in the placebo group than the vaccinated group, the study population may not be comparable to the general New Zealand population aged 65 to 80 years of age.

2.12.4. Winje et al. Norwegian Institute of Public Health. 2019: a review of the efficacy and effectiveness of pneumococcal vaccination (PPV23 and PCV13) in older adults conducted by Norwegian, Swedish and Danish Public Health Institutes. The Committee noted that the randomised controlled trials included in the analysis resulted in a pooled vaccine effectiveness of 76% (95% CI -18% to 95%; I-squared=0%), which is not statistically significant evidence of effectiveness. The pooled vaccine effectiveness from the included cohort studies for the prevention of IPD was 62% (95% CI 37% to 76%; I-squared=24%), including some studies with methodological limitations.

2.12.5. Berild et al. Pathogens. 2020;9:259: a systematic review of studies published between 2016 and 2019 on the effectiveness and efficacy of pneumococcal vaccination (PPV 12 and PPV23) on pneumonia and invasive pneumococcal disease in an elderly population. The Committee noted that vaccine efficacy ranging from 3% to 16% against all cause pneumonia, and 50% for IPD (95% CI 15% to 74%) was reported.

2.12.6. Htar et al. PLoS One. 2017;12:e0177985: a systematic review and meta-analyses of non-experimental observational studies assessing pneumococcal vaccine effectiveness against community-acquired pneumonia in adults among the general population, the immunocompromised and subjects with underlying risk factors in real-world settings. The Committee noted that 33 studies were included, and all participants were over 18 years of age. The Committee noted that vaccine effectiveness in those with community acquired pneumonia over 64 years of age ranged widely from -143% to 60%. The Committee also noted that the meta-analysis estimating vaccine efficacy for any community acquired pneumonia requiring hospitalisation in the general population gave a figure of 10.2% (95% CI -12.6 to 33.0), and that vaccine efficacy for NBPP ranged from 39% to 42% in adults aged 50 years or older in the general population.

2.12.7. Menzies et al. Med J Aust. 2014;200:112-5: an ecological analysis of trends in IPD notification rates and vaccine effectiveness using data on Australians aged ≥ 65 years (23vPPV funded) and 50-64 years (23vPPV not funded). The Committee noted that the incidence rate ratio for total IPD was 0.65 (95% CI 0.59 to 0.71) for people aged ≥ 65 years, and 0.80 (95% CI 0.71 to 0.90) for people aged 50-64 years. The estimate of 23vPPV effectiveness was 61.1% (95% CI 55.1% to 66.9%).

2.12.8. Ahn et al. Vaccine. 2015; 33:4770-4775: an evaluation of immune response in 62 participants over the age of 65 (Group 1 aged 65 to 74 years, and Group 2 aged 75 or over), measuring serotype-specific anti-pneumococcal antibodies with opsonophagocytic assay. Geometric mean titres to all tested serotypes significantly increased in both groups after vaccination compared to those before

vaccination (P<0.001 for all). The Committee noted that study only evaluates immune response rather than more relevant outcomes.

2.12.9. Baldo et al. PLoS One. 2016;11:e0166637: a retrospective analysis on the mortality rates after a first hospitalisation for community acquired pneumonia in those 65 years of age or over, especially focusing on the role of pneumococcal vaccination as a risk factor associated with pneumonia-related mortality at one year. The Committee noted that of the 4030 people hospitalised with community acquired pneumonia, 3241 had not been vaccinated, 583 had PPV23, and 206 had PCV 13. The Committee noted that death specifically due to pneumonia had a rate of 10.7% (95% CI 6.5% to 14.9%), which was lower than in the unvaccinated or PPV23 groups, with 16.4% (95% CI 15.1% to 17.7%) and 14.1% (95% CI 11.2% to 16.9%), respectively. The Committee also noted that survival rates 1 year after hospitalisation were greatest in the PCV13 group, with survival rates at 1-year after hospitalisation of 83.6%, 85.9% and 89.3% in the unvaccinated, PPV23 and PCV13 groups, respectively. However, the Committee noted that the PCV13 group was very small and that no microbial data was collected so it clear whether the pneumonia cases were caused by pneumococcal or other bacteria.

2.12.10. Schiffner-Rohe et al. PLoS One. 2016;11:e0146338: a meta-analysis of randomised controlled trials to investigate the effect of PPV23 for preventing community acquired pneumonia in adults 60 years of age or older. The Committee noted that overall, the study concluded that there is no evidence that PPV23 can prevent NBPP in a general, community dwelling population.

2.13. The Committee considered the evidence for PPV23 against pneumococcal infection in those aged over 65 to be of poor quality and mixed strength, with low-moderate, inconclusive evidence of efficacy against PPV23 serotypes and IPD, and low-quality evidence and imprecise results for the efficacy of PPV23 against NBPP. The Committee noted that effectiveness was not demonstrated to be consistent in the general population, and that the meta-analyses reported a wide range of effectiveness estimates.

2.14. The Committee noted that its past advice was that PPV23 is effective against IPD, and that more robust evidence is needed to show efficacy against NBPP. The Committee considered that the evidence presented for PPV23 against NBPP is imprecise and of low quality. The Committee noted that although there appears to be limited benefit with PPV23, there would be no additional clinical risk to widening access, and no non-clinical features of the vaccine that would impact on its use by healthcare workers that are different to other vaccines.

2.15. The Committee considered that it is reasonable to assume that uptake of the PPV23 in people aged 65 years of age and older would unlikely be higher than influenza vaccine, however, due to COVID-19 the uptake of influenza vaccine increased in 2020. The Committee also noted that the PPV23 vaccine can be administered at the same time as influenza vaccine, and that uptake may be affected if patients receive both at the same visit.

2.16. The Committee noted that data for IPD incidence and mortality show higher rates in those younger than 65 years of age, and in Māori and Pacific populations. The Committee also noted that community acquired pneumonia is more common in those over 70 years of age, and not younger than 65 years. Noting the IPD incidence data for the New Zealand population, the Committee considered that the patient population that might benefit the most from receiving PPV23 are Māori and Pacific people younger than 65 years of age, who have chronic underlying health conditions. The Committee requested the Immunisation Subcommittee's view on the patient population that would benefit most from this vaccine.

2.17. The Committee noted that the response to immunisations in older adults wanes over time due to immunosenescence. Therefore, the Committee considered that there may be a need for repeat dosing requested the Immunisation Subcommittee's advice on this, especially

considering that the most at-risk age group for community acquired pneumonia is those over 70 years of age.

2.18. The Committee noted that the correct comparator for the New Zealand context is standard care without funded immunisation (similar to the placebo arms of controlled trials), but that this may change over time if the availability of current PCV vaccine (PCV13) and new pneumococcal conjugate vaccines undergoing clinical trials (PCV15, PCV20) changes. The Committee noted that if the PPV23 vaccine was effective in preventing IPD and NBPP, then reduced hospital admissions would lead to overall savings for the health sector, however due to the lack of reporting of NBPP hospital admissions, the actual impact and cost to the health sector is currently unknown.

2.19. The Committee noted that the supplier has assumed in its application that that NBPP serotype rates match those of IPD. The Committee considered that it had not seen evidence to support this, and that the disease depends not only on serotypes but on the pathogen-host interaction (Song et al. J Korean Med Sci. 2013;28:4-15).

2.20. The Committee considered that future economic modelling for PPV23 would need to be based on IPD incidence across population and age groups, due to the lack of robust NBPP data. The Committee also considered that any economic modelling should be undertaken following receipt of additional advice from the Immunisation Subcommittee about the most appropriate population groups.

3. Horizon scan: Medicinal cannabis

Background

3.1 The Committee noted that, in August 2015, PTAC considered the funding of cannabidiol with tetrahydrocannabinol (Sativex) for multiple sclerosis-related spasticity, pain (including pain associated with spasticity) and treatment-refractory epilepsy. At that time, PTAC had recommended funding be declined for each of these indications (refer to the August 2015 PTAC meeting record for detail of PTAC's consideration and recommendations).

3.2 The Committee noted that PHARMAC has not received further information regarding Sativex, nor have PHARMAC received any further funding applications for any medicinal cannabis products for any indications.

3.3 The Committee noted that Named Patient Pharmaceutical Assessment (NPPA) applications have been received by PHARMAC since 2013 for medicinal cannabis products for a range of indications.

3.4 The Committee noted that PHARMAC was seeking updated advice from the Committee regarding the current, overall, landscape of evidence for medicinal cannabis, in the form of an overarching horizon scan.

3.5 The Committee noted that, for the purposes of this horizon scan, there was no comprehensive collection nor review of evidence from the large amount of the clinical data for multiple products and multiple clinical indications and settings. In turn, the Committee had not undertaken formal critical appraisal of individual publications, reviews or international and local jurisdictions/funders' evidence appraisals, nor had the Committee undertaken any systematic reviews itself.

Discussion

Medicinal cannabis products and Medsafe approval

3.6 The Committee noted that the term medicinal cannabis describes a prescription-only plant component, extract or processed product e.g. tablet, capsule or liquid, for therapeutic use

that is derived from *Cannabis sativa*, which contains over 100 cannabinoid compounds. The Committee noted that its two main compounds are cannabidiol (CBD) and tetrahydrocannabinol (THC) and that in NZ any medicinal cannabis product's dosage must define and numerically specify its component compounds (Medicinal Cannabis Agency, Ministry of Health. 2020). For the purpose of this discussion, synthetic products were not discussed.

3.7 The Committee noted that CBD and/or THC may be present in variable amounts and proportions within medicinal cannabis products, although the amount of THC within the product must not exceed the amount specified in the Misuse of Drugs Act 1975 (Section 2A).

3.8 The Committee considered that medicinal cannabis products should be considered on an individual basis due to variation in their production, quality and component compounds. The Committee noted that mass spectrometry can identify different cannabinoids and concentrations, and can also check for toxic components within the product such as heavy metals, additives and insecticides.

3.9 The Committee noted that only one medicinal cannabis product is currently approved by Medsafe in New Zealand (cannabidiol with tetrahydrocannabinol, brand name Sativex [2.7 mg THC and 2.5 mg CBD per 100 microlitres]), which is formulated as an oromucosal spray (Medsafe, 2020). The Committee noted that Sativex is classified as a Class B1 controlled drug and is approved by Medsafe as an add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

3.10 The Committee noted that no other products containing cannabinoids appear to be seeking Medsafe approval or are Medsafe-approved for distribution in New Zealand at this time.

Future funding applications

3.11 The Committee noted from the Guidelines for Funding Applications to PHARMAC that funding applications to PHARMAC should be for products in specific indications that have already been Medsafe-approved, with the exception of medicines for cancer; where applications may be assessed by PHARMAC in parallel to Medsafe assessment, or medicines for rare disorders; which, if not Medsafe-approved, may be considered if an international regulatory authority has approved the medicine for the specific indication or condition.

3.12 The Committee considered that products without Medsafe approval do not have the benefit of Medsafe's assessment of the product's content, quality, production, and safety; including long-term risks. The Committee considered that Medsafe approval is particularly important for medicinal cannabis products that are considered by PHARMAC for funding, due to safety considerations.

3.13 The Committee noted that a funding application for a medicinal cannabis product should meet PHARMAC's requirements as detailed in the Guidelines for Funding Applications to PHARMAC, in order to provide sufficient information for evidence-based assessment and appraisal. In particular, the Committee considered that the specific patient population and the symptoms (or disease itself) intended to be treated should be clearly and appropriately defined. The Committee considered that an application to fund a medicinal cannabis product ideally should include a specific Medsafe-approved product supported by randomised controlled trials, with an appropriate comparator in a generalisable patient sample, and including long-term outcome and safety data.

Body of evidence for medicinal cannabis and international experience

3.14 The Committee noted that the body of available evidence for medicinal cannabis was varied and sizeable, including pre-clinical and clinical studies in a wide range of indications, doses, formulations and types and combinations of cannabinoids. The Committee noted summaries of evidence included in Cochrane reviews, other systematic reviews and meta-analyses, for a variety of indications.

3.15 However, the Committee considered that in many indications, including chronic pain which was the subject of a very recent review (International Association for the Study of Pain presidential task force on cannabis and cannabinoid analgesia. PAIN; 2021: doi: 10.1097/j.pain.0000000000002265), that the clinical evidence appeared to be of poor/low quality with methodological issues e.g. study design, and appeared generally insufficient to support a benefit from treatment in most indications. In particular, the Committee noted that the evidence appeared to include short-term clinical trials that may not capture relevant long-term safety signals, and evidence in settings e.g. nausea, where improved clinical management has changed the clinical need over time.

3.16 The Committee noted that very few international jurisdictions have recommended medicinal cannabis products be funded. The Committee noted that, since PTAC's assessment of Sativex in 2015, England and Wales (NICE) had reviewed evidence that appeared to be of reasonable quality for cannabidiol (Epidyolex: 100mg/ml CBD) in conjunction with clobazam in patients with paediatric epilepsy syndromes and had recommended cannabidiol as a treatment option for these rare syndromes (NICE December 2019a; NICE December 2019b). The Committee considered that the submission reviewed by NICE was supported by evidence which, if accompanied by the appropriate application content, may meet PHARMAC's application requirements.

3.17 Members considered that many international jurisdictions were struggling with both the expanding body of generally poor-quality evidence alongside challenges associated with rapid implementation of medicinal cannabis for therapeutic use. The Committee noted that in some countries, medicinal cannabis has not led to an expected reduction in the use of other drugs e.g. opioids. However, members considered that the cause and effects of international opioid and cannabinoid usage can be difficult to determine due to cannabis use being legalised at the same time as opioid de-prescribing policies have come into practice. The Committee considered that efforts to streamline medicinal cannabis evidence and knowledge sharing e.g. international peer-reviewed and published data summaries, should be used by PHARMAC, PTAC and Subcommittees wherever possible, given the varied and broad body of evidence. Members considered that prescribing guidance could be unreasonably influenced by product advocates.

Potential risks from medicinal cannabis

3.18 The Committee considered that the body of evidence suggests that medicinal cannabis is associated with more adverse effects than placebo and that CBD is associated with anxiety, sleepiness and gastrointestinal effects. The Committee considered that, although most effects are generally minor, some events can be severe and may have serious consequences. The Committee noted that the use of THC in young people can result in chronic psychotic disorders, which are complicated to manage and can result in significant harm, despite such disorders having relatively low incidence.

3.19 The Committee also noted that there is emerging evidence of dose-dependent effects, including drug interactions due to metabolism and psychoactive effects of the lipophilic medicinal cannabis products, and considered that drug interactions in particular could be challenging to safely manage in patients with chronic conditions who receive a number of medications. In particular, members noted that a diminished effect from cancer immunotherapy had been observed when medicinal cannabis was used in combination.

3.20 Members noted that there is emerging anecdotal evidence that long-term adverse effects from medicinal cannabis are often not formally reported to international medicine regulators

and that this issue is exacerbated when products are not approved by the regulator. The Committee considered that long-term safety information did not appear to be well captured in the clinical trial evidence due to the short duration of many trials. Overall, the Committee considered that the evidence for the safety of medicinal cannabis was likely to underestimate long-term risks.

Health needs of New Zealand people

3.21 The Committee noted that patients may experience a health need due to issues accessing effective treatments or having tried all the funded alternative treatments e.g. in end-stage disease or disease that is refractory to accessible therapies, or have uncontrolled symptoms despite accessible treatments.

3.22 The Committee noted the NPPA applications received to date by PHARMAC for medicinal cannabis. The Committee considered that there may be an unmet need for effective, accessible therapy and therefore there may be an interest in the use of medicinal cannabis in (but not necessarily limited to) people with the following conditions: degenerative conditions; epilepsy (including paediatric epilepsy); chronic mental health conditions e.g. PTSD or severe anxiety; chronic pain including neuropathic pain; spasticity associated with multiple sclerosis; and autoimmune diseases including multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and chronic fatigue syndrome.

3.23 The Committee reiterated its view that the evidence for medicinal cannabis appeared generally insufficient to support a benefit from treatment in most indications.

Medicinal cannabis in New Zealand

3.24 Members considered that a small subset of New Zealand prescribers were represented in requests for access to medicinal cannabis products, which may reflect low levels of confidence in the evidence base for its benefits and risks, alongside the high cost of the only product available in New Zealand and the regulatory restrictions for prescribing. Members considered that due to substantial interest in recreational use and expected levels of company sponsorship, that overprescribing could become an issue. The Committee considered that there is a significant potential risk of harm from medicinal cannabis if not prescribed and used appropriately i.e. according to high quality clinical evidence.

3.25 The Committee considered that the definition, risks and optimal use of medicinal cannabis is generally not well understood by the New Zealand general public. The Committee considered that many people prescribed medicinal cannabis would incorrectly consider that they could obtain any form of cannabis on their own from any source i.e. instead of obtaining a regulated medicinal cannabis product from a pharmacy. The Committee considered that in addition to being sought for use in specific conditions, medicinal cannabis might be accessed to relieve complaints such as insomnia and anxiety, for which non-pharmacological management might be more appropriate, such as life-style and other non-medication interventions.

3.26 The Committee considered that challenges relating to use of medicinal cannabis in New Zealand would include effects for patients expecting to switch from smoking cannabis to medicinal cannabis and implications for driving and workplace activities. Members noted that there is currently no threshold or functional assessment within New Zealand to determine a person's inability to drive due to effects of CBD and/or THC and no easily portable method to distinguish effects from smoking cannabis compared to medicinal cannabis. The Committee noted that the New Zealand Transport Authority (NZTA) is currently reviewing its advice regarding this issue.

3.27 The Committee noted that a Medsafe-approved medicinal cannabis product would be required in order to enable ongoing collection of safety data from use in New Zealand, and

considered that long-term effects would likely be greater than reported in the available evidence.

Costs associated with medicinal cannabis

3.28 The Committee noted that patients who currently self-fund access to medicinal cannabis incur costs due to consultation and follow-up visits, in addition to the product cost itself.

3.29 The Committee considered that it was unclear what benefit should be assigned to euphoria from medicinal cannabis for cost-effectiveness modelling, as opposed to an objective measurement of benefit which may be used in modelling for other treatments. In addition, the Committee noted the difficulty in modelling benefits from poor quality evidence and considered that assessment of cost-effectiveness of medicinal cannabis products would likely be driven by price.

Closing

3.30 The Committee considered that although the evidence for medicinal cannabis spans a wide range of conditions, the evidence generally appeared to be of low quality, did not sufficiently capture long-term risks and appeared generally insufficient to support a benefit from treatment in most indications. The Committee considered that the poor evidence base, insufficient knowledge of safety concerns, and challenges associated with appropriate use in New Zealand may lead to a risk of harm from medicinal cannabis.

3.31 In summary, the Committee noted that any future funding applications for medicinal cannabis products should meet PHARMAC's application requirements, including a specific Medsafe-approved product supported by randomised controlled trials, with an appropriate comparator in a generalisable patient sample, and providing long-term safety data. The Committee would welcome any application for a Medsafe approved medicinal cannabis product that meets PHARMAC requirements and is supported by quality evidence.
