Record of the Mental Health Subcommittee of PTAC Meeting held on 10 September 2021

Mental Health Subcommittee 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 Mental Health Subcommittee meeting; only the relevant portions of the meeting record relating to Mental Health Subcommittee discussions about an Application or Pharmac staff proposal that contain a recommendation are generally published.

The Mental Health 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.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

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

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

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

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1. Attendance

Present

Sean Hanna (Chair)
Alan Fraser
Bronwyn Copeland
Cathy Stephenson
David Chinn
Prof David Menkes
Giles Newton-Howes
Jeremy McMinn
Verity Humberstone

2. The role of PTAC Subcommittees and records of meetings

2.1. This meeting record of the Mental Health 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.

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

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

2.4. The Mental Health Subcommittee is a Subcommittee of PTAC. The Mental Health Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Mental Health Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for Mental Health that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Mental Health that differ from the Mental Health Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

Pharmac considers the recommendations provided by both the Mental Health Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for Mental Health.

3. Aripiprazole depot - schizophrenia

Application

3.1. The Subcommittee reviewed additional information regarding the funding application for aripiprazole depot for the treatment of schizophrenia.

Recommendation

3.1. The Subcommittee **recommended** that aripiprazole depot be listed with a **medium priority** within the context of treatments in mental health, subject to the following Special Authority criteria:

> Initial application from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
>
> Both:
> 1 The patient has or is at high risk of metabolic syndrome; and
> 2 Either:
> 2.1 The patient has had an initial Special Authority approval for risperidone depot injection, paliperidone depot injection or olanzapine depot injection; or
> 2.2 All of the following:
> 2.2.1 The patient has schizophrenia; and
> 2.2.2 The patient has received treatment with oral atypical antipsychotic agents but has been unable to adhere; and
> 2.2.3 The patient has been admitted to hospital or treated in respite care, or intensive outpatient or home-based treatment for 30 days or more in last 12 months.

Renewal from any relevant practitioner. Approvals valid for 12 months where the initiation of aripiprazole depot injection has been associated with fewer days of intensive intervention compared with pre-aripiprazole depot initiation.

3.2. In making this recommendation, the Subcommittee considered the high health need of individuals with schizophrenia, the health need of Māori and Pacific peoples, and the current high cost of aripiprazole depot.

3.3. PTAC and PTAC Subcommittees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives.

Discussion

3.4. The Subcommittee noted that the funding application for aripiprazole depot for schizophrenia was reviewed by PTAC in 2015 and received a cost neutral recommendation to paliperidone, according to specific funding criteria.

3.5. The Subcommittee noted additional information had been submitted to Pharmac from a range of healthcare professionals, including a number of submissions in support of the funding of aripiprazole depot.

3.6. The Subcommittee noted that people with schizophrenia have a varying range of health need, but in general have substantial health needs, both mental and physical. The Subcommittee noted that on average, people with schizophrenia often die 10 years earlier than the general population, often through cardiovascular mortality.

3.7. The Subcommittee noted there are currently 13 oral and six depot antipsychotic agents funded. The Subcommittee considered that while there are a number of treatment options, the available agents are limited by side effects - mainly extrapyramidal and metabolic. Members noted the substantial impacts. The Subcommittee considered that there are issues in access to these pharmaceuticals, particularly in regard to adherence related to intolerable side effects. The Subcommittee considered that adherence was likely to differ between patient subpopulations, with those with poor insight and/or motivation (likeliest to be features of the underlying disease itself) more prone to nonadherence.

3.8. The Subcommittee considered, given the side effect profile of currently available treatments there is a considerable side-effect burden on patients. The Subcommittee noted that Māori and Pacific people have higher rates of schizophrenia than the general population.

3.9. The Subcommittee considered that while schizophrenia treatment rates between Māori and non-Māori are generally comparable, there is a significant issue with Māori presenting more in acute settings through inpatient services, presenting substantially more unwell and receiving treatment later than the general schizophrenia population. Members considered that while this is unlikely to impact the net result of treatment, it is far from ideal as early recognition and intervention may prevent some of the acute outcomes.

3.10. Members considered that compared with treatment received by the general schizophrenia population in New Zealand, there is currently a high rate of clozapine use in Māori for a variety of reasons, but generally associated with the higher rate of acute presentation. However, that this higher clozapine use in Māori is aligned more closely with international treatment guidelines for schizophrenia.

Members considered that, anecdotally, Māori have higher rates of treatment resistant schizophrenia than the general NZ population.

3.11. The Subcommittee noted that a number of people receive treatment with antipsychotics under the Mental Health Act. The Subcommittee considered that with currently funded treatments, this means that many patients experience a number of comorbidities and adverse effects resulting from treatment, in circumstances where patients are obliged to accept compulsory treatment.

3.12. The Subcommittee noted a comparative study on the effect of 18 antipsychotics on metabolic function in patients with schizophrenia (Pillinger et al. Lancet Psych. 2020;7:64-77). The Subcommittee noted there were clear metabolic advantages demonstrated with aripiprazole compared with other antipsychotic agents such as olanzapine and clozapine.

3.13. The Subcommittee considered that aripiprazole provides strong additional benefits above currently funded antipsychotic agents. The Subcommittee noted that aripiprazole has a relatively benign metabolic profile compared to currently available depot antipsychotics, possibly better efficacy against the negative symptoms of schizophrenia (eg. as reported in Robinson et al. Schizophrenia Bulletin. 2015;41:1227-36 compared with risperidone), is useful as an adjuvant treatment in patients receiving clozapine, and may also have useful co-antidepressant activity.

3.14. Members noted that hyperprolactinemia is a common side effect of antipsychotic treatment and often manifests as sexual dysfunction. Members considered that this can often negatively impact adherence to treatment, particularly for paliperidone. The Subcommittee were made aware of an article that reported that risperidone, paliperidone, amisulpride and haloperidol were associated with the worst outcomes related to hyperprolactinemia while aripiprazole was associated with more preferable outcomes (Stroup and Gray. World Pysch 2018;17:341-56).

3.15. The Subcommittee noted the results of an unblinded randomised clinical trial which investigated the use of aripiprazole once monthly injections compared with clinician's choice (which included other depot treatment options) (Kane et al. JAMA Psychiatry. 2020;77:1217-24). The Subcommittee noted that the time to first hospitalisation favoured aripiprazole depot, hazard ratio: 0.56 (95% CI: 0.34-0.92; P=0.02).

3.16. The Subcommittee noted that of the six currently funded antipsychotic depot agents, only haloperidol and paliperidone are administered monthly, while other agents are administered more regularly. The Subcommittee considered that the addition of aripiprazole depot, as a monthly injection would be a significant advantage to a number of patients.

3.17. The Subcommittee noted that additional risks related to aripiprazole depot include akathisia and that compared with risperidone and olanzapine, presentations of psychosis may be more common. Members noted that akathisia is a serious side effect and would need to be adequately monitored, managed and supported in practice, noting that the depot formulation creates more difficulties compared with oral in relation to reactive dosing changes.

3.18. Members also noted that aripiprazole may have lower efficacy compared with some other agents (as described in the direct and indirect comparison meta-analysis Leucht et al. Lancet. 2013;382:951-62), and as such if patients were

transitioned from these agents to aripiprazole depot, they may experience reduced efficacy, particularly in acute schizophrenia compared with olanzapine and risperidone.

3.19. On balance of the available evidence, Members considered that despite its at times lower efficacy, the more favourable side effect profile of aripiprazole depot and the likely positive impact on adherence, compared with currently funded agents, was likely to result in better health outcomes for a number of people with schizophrenia.

3.20. The Subcommittee considered that those who would benefit most from aripiprazole depot include: (1) people responding well to oral aripiprazole but for whom adherence is a challenge; and (2) people requiring depot antipsychotics but whom have, or are at risk of severe metabolic side effects. The Subcommittee noted that Māori have higher rates of metabolic syndrome, diabetes, and cardiovascular disease, and as such are particularly likely to benefit from aripiprazole depot.

3.21. The Subcommittee considered that if aripiprazole depot were funded for schizophrenia, uptake would be moderate. Members estimated that at least 10% of patients on oral aripiprazole (however likely higher), 5-10% on first generation depot agents and 15-20% of patients on second generation depot agents would transition to aripiprazole depot. Members considered that very few patients would likely shift from other oral antipsychotic agents. The Subcommittee considered that the use of oral aripiprazole would likely increase if the depot formulation were funded.

3.22. Members considered that aripiprazole depot would likely be a preferable treatment option in early settings, with higher uptake in younger individuals (eg. teens to twenties).

3.23. Members noted there may be benefit of aripiprazole depot in other indications such as bipolar affective disorder or treatment-resistant major depression, but that these were off-label indications and that a funding application had not been received for either of these indications.

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

Population	People with schizophrenia, with or at high risk of metabolic syndrome and unable to adhere to currently funded oral antipsychotics.
Intervention	Aripiprazole depot, 400 mg every 28 days.
Comparator(s)	First generation antipsychotics (14% to 22%) Second generation antipsychotics (43% to 44%) Oral antipsychotics (22% to 29%) Other oral antipsychotics (11% to 14%)
Outcome(s)	Improved adherence Improved metabolic outcomes Treatment associated side effects Long term impact on cardiovascular disease and diabetic risk Quality of life Health sector costs/savings
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

4. Buprenorphine depot (Buvidal and Sublocade) – opioid use disorder

Application

4.1. The Subcommittee reviewed an application from Camurus for the use of buprenorphine depot injection (Buvidal weekly and Buvidal monthly) for the maintenance treatment of patients with opioid dependence; and

4.2. The Subcommittee reviewed an application from Indivior for the use of buprenorphine depot injection (Sublocade) for the treatment of opioid use disorder.

Recommendation

4.3. The Subcommittee **recommended** that the Buvidal brand buprenorphine depot be funded with a **high priority** within the context of treatments in mental health, subject to the following Special Authority criteria:

> INITIAL APPLICATION. Applications from any relevant practitioner. Approvals valid for 12 months.
> All of the following:
> 1 Patient is opioid dependent, and
> 2 Patient has been stabilised on buprenorphine with naloxone, and
> 3 Patient is currently enrolled in an opioid substitution program in a service approved by the Ministry of Health, and
> 4 Applicant works in an opioid treatment service approved by the Ministry of Health or is a medical practitioner authorised by the service to manage treatment in this patient.
>
> RENEWAL APPLICATION. Applications from any relevant practitioner. Approvals valid for 12 months.
> All of the following:
> 1 Treatment remains appropriate and patient is benefitting from treatment.
> 2 Patient is or has been receiving maintenance therapy with buprenorphine depot injection (and is not receiving methadone), and
> 3 Patient is currently enrolled in an opioid substitution program in a service approved by the Ministry of Health, and
> 4 Applicant works in an opioid treatment service approved by the Ministry of Health or is a medical practitioner authorised by the service to manage treatment in this patient.

4.4. The Subcommittee recommended that the Sublocade brand buprenorphine depot be funded with a **high priority** within the context of treatments in mental health, subject to the following Special Authority criteria:

> INITIAL APPLICATION. Applications from any relevant practitioner. Approvals valid for 12 months.
> All of the following:
> 1 Patient is opioid dependent, and
> 2 Patient has been stabilised on buprenorphine with naloxone, and
> 3 Patient is currently enrolled in an opioid substitution program in a service approved by the Ministry of Health, and
> 4 Applicant works in an opioid treatment service approved by the Ministry of Health or is a medical practitioner authorised by the service to manage treatment in this patient.
>
> RENEWAL APPLICATION. Applications from any relevant practitioner. Approvals valid for 12 months.
> All of the following:
> 1 Treatment remains appropriate and patient is benefitting from treatment.
> 2 Patient is or has been receiving maintenance therapy with buprenorphine depot injection (and is not receiving methadone), and
> 3 Patient is currently enrolled in an opioid substitution program in a service approved by the Ministry of Health, and
> 4 Applicant works in an opioid treatment service approved by the Ministry of Health or is a medical practitioner authorised by the service to manage treatment in this patient.

4.5. In making these recommendations, the Subcommittee considered the high health need of individuals with opioid use disorder, the unquantified but likely health related quality of life benefit from buprenorphine depot, and the benefit and moderate to significant cost savings to wider society.

4.6. The Subcommittee considered that Buvidal and Sublocade were equivalent for the treatment of opioid use disorder. The Subcommittee considered it would be appropriate to fund only one buprenorphine depot product.

Discussion

4.7. The Subcommittee noted that opioid use disorder is a chronic, relapsing and remitting condition that is characterised by the compulsive self-administration of opioid substances for non-medical uses or their administration in excessive doses (Sellman. Addiction. 2010;105:6-13). The Subcommittee noted that it is associated with significantly increased rates of morbidity and mortality.

4.8. The Subcommittee noted that according to the 2016 New Zealand Drug Harm report (Ministry of Health, 2016), approximately 2000 people in New Zealand have opioid use disorder, however members considered that this is likely an underestimate as over 5000 individuals receive opioid substitution treatment each year. The Subcommittee noted there are approximately 10 direct deaths from opioid drug use each year in New Zealand, the majority of which are avoidable (Degenhardt et al. Addiction. 2014,10990-9).

4.9. The Subcommittee considered people with opioid use disorder have a high health need, noting the high morbidity and mortality rate (Bell et al. Addiction. 2009;104:1193-200; Degenhardt et al. Addiction. 2011;106:32-51), increased infection rates compared with the general population, and social implications of opioid use disorder.

4.10. The Subcommittee considered the health need of family and whānau of people with opioid use disorder can be significant and become more serious over time.

The Subcommittee also considered that opioid use disorder results in a large cost to society, with opioid use disorder carrying an increased likelihood of criminal justice system involvement and negative outcomes on, employment, health, residential stability, education and child welfare (Fairley et al. JAMA Psych. 2021;78:767-77).

4.11. The Subcommittee noted the 2006 NZ Mental Health Survey data, which reported that substance use disorder as higher for Māori at 6.0% compared with Pacific people, 3.2% and others, 3.0% (Ministry of Health, 2006). Members considered that individuals with low socioeconomic status, prisoners, remote populations and individuals with mental illness are also disproportionally affected by opioid use disorder.

4.12. The Subcommittee noted that sublingual buprenorphine with naloxone and methadone are currently funded and used in the treatment of opioid use disorder, in conjunction with medical, social and psychological support. The Subcommittee considered that there are currently issues with access to and availability of treatments for opioid use disorder. Members considered that healthcare professional staffing resource (including specialists), access to pharmacies, stigma, discrimination and social inequity all impact the accessibility of treatment.

4.13. The Subcommittee noted that buprenorphine is a μ (mu) opioid receptor partial agonist, and κ (kappa) opioid receptor antagonist, with its activity in opioid maintenance treatment attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. The Subcommittee noted that this creates a “ceiling” effect that limits the risk of overdose while reducing opioid cravings and withdrawal symptoms. The Subcommittee considered that the mechanism of action meant that buprenorphine depot reduces the risk of accidental opioid overdose, is safer than and avoids some of the side effects associated with methadone.

4.14. The Subcommittee noted that buprenorphine is classified as a Class C4 controlled drug and both Sublocade and Buvidal require medical, social and psychological support as per their Medsafe approval.

4.15. The Subcommittee noted that there were two funding applications under consideration – Buvidal and Sublocade, both buprenorphine depot formulations.

Buvidal

4.16. The Subcommittee noted that Buvidal can be administered weekly or monthly and administered into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. The Subcommittee noted that the recommended starting dose of Buvidal is 16 mg weekly, with one or two additional 8 mg doses at least one day apart, to a target dose of 24 mg or 32 mg during the first treatment week, with a recommended dose for the second treatment week being the total dose administered during the week of initiation. The Subcommittee noted that the monthly formulation then may be started and that clients can switch between the weekly and monthly formulations.

4.17. The Subcommittee noted that Buvidal is non-inferior to sublingual buprenorphine with naloxone. The Subcommittee noted the randomised, double-blind, double-dummy, active-controlled trial which investigated sublingual placebo plus weekly / monthly buprenorphine depot, compared with sublingual buprenorphine with naloxone plus weekly/monthly placebo injections in individuals with opioid use

disorder for 24 weeks (Lofwall et al. JAMA int med. 2018;178(6):764-773). The Subcommittee noted that the group treated with buprenorphine depot demonstrated a statistically significant greater response rate compared with the sublingual buprenorphine with naloxone group (3.0% difference (95% CI: −4.0% to 9.9%; P<0.001); while those treated with buprenorphine depot also demonstrated a statistically significant difference in opioid-negative urine samples (6.7% difference, 95% CI: ,−0.1% to 13.6%; P<0.001).

4.18. The Subcommittee considered that the non-inferiority evidence for Buvidal was strong and demonstrated that buprenorphine depot was comparable to sublingual buprenorphine with naloxone.

4.19. The Subcommittee also noted the following evidence:

- Lintzeris et al. JAMA Netw Open. 2021.4(5):e219041
- Frost et al. Addiction. 2019;114(8):1416-1426

Sublocade

4.20. The Subcommittee noted that the recommended dose of Sublocade is 300 mg monthly for the first two months, followed by a maintenance dose of 100 mg monthly or 300 mg monthly for patients who tolerate the 100 mg dose, but do not demonstrate a satisfactory clinical response. The Subcommittee noted that Sublocade is administered via abdominal subcutaneous injection.

4.21. The Subcommittee noted a randomised, double blind, placebo-controlled trial that investigated buprenorphine depot compared with placebo in individuals with moderate of severe opioid use disorder for six months (Haight et al. Lancet. 2019;393:778-90). The Subcommittee noted the primary outcome of opioid abstinence was significantly greater in those treated with buprenorphine depot compared with placebo. The Subcommittee noted that the safety profile was consistent with other buprenorphine products. The Subcommittee considered that there did not appear to be an additional benefit from the 300 mg dose in comparison to the 100 mg dose.

4.22. The Subcommittee also noted the following evidence:

- Andorn et al. J Clin Psychopharmacol. 2020;40:231-9
- Ling et al. J Subst Abuse Treat. 2020;110:1-8

General

4.23. The Subcommittee considered that the evidence of benefit of buprenorphine depot for opioid use disorder was of good strength, with good benefit shown, both compared with placebo and as non-inferior to sublingual buprenorphine with naloxone. The Subcommittee considered that the evidence was highly relevant to the New Zealand setting.

4.24. The Subcommittee considered that the evidence suggested that buprenorphine depot would maintain clients on treatment, which over time would result in additional benefits to those observed in the trials. The Subcommittee considered

that these data would be best demonstrated in population-based cohort studies with long follow up.

4.25. The Subcommittee noted that there was not currently any health-related quality of life evidence for buprenorphine depot, however considered it reasonable to assume that treatment with buprenorphine depot would result in improved health related quality of life.

4.26. The Subcommittee also considered that buprenorphine depot would provide benefits to individuals and their whānau from minimised diversion, less pharmacy visits, steady state effect and a more favourable safety profile than methadone.

4.27. The Subcommittee considered that buprenorphine depot would likely improve adherence compared with sublingual buprenorphine with naloxone, but would require appropriate patients to be initiated on depot treatment.

4.28. The Subcommittee noted that buprenorphine with naloxone sublingual tablets and methadone are commonly dispensed daily in community pharmacies, and the availability of an alternative treatment would likely reduce these pharmacy visits. The Subcommittee noted that buprenorphine depot would require administration by a healthcare professional once per week or month (depending on brand). The Subcommittee noted that this difference would mean that adaptations in the mechanisms by which treatment is delivered may be necessary.

4.29. The Subcommittee considered it was unclear where buprenorphine depot would be administered to patients, with options including Community Alcohol and Drug Services, community pharmacies and general practice. The Subcommittee considered that if a client were to receive their depot in general practice, the cost of the injection would fall to clients, and as such members considered that the majority of clients (at least initially) would receive their treatment at Community Alcohol and Drug Services. The Subcommittee considered that this would add to those services' already overloaded workloads. The Subcommittee considered that the cost of administration should be included in the cost analysis for the healthcare system.

4.30. The Subcommittee considered that the availability of buprenorphine depot would be unlikely to reduce the number of visits a client has with health care services (with the exception of pharmacy for daily pickup). Members considered that the availability of buprenorphine depot may increase referrals to Community Alcohol and Drug services.

4.31. The Subcommittee considered that buprenorphine depot had a large suitability benefit compared with currently funded oral buprenorphine with naloxone and methadone, for both the individual and their whānau, particularly in regard to the less regular administration. The Subcommittee considered that buprenorphine depot was highly likely to provide substantial benefit in rural communities and for individuals having difficulty remaining in employment, where daily access to a pharmacy can provide a significant barrier to current treatment access.

4.32. The Subcommittee considered that the different dosing schedules of Sublocade and Buvidal were unlikely to cause any additional advantages or disadvantages. The Subcommittee noted that the requirement of cold chain storage of Sublocade may result in additional health sector costs.

4.33. The Subcommittee considered that those who would benefit most from buprenorphine depot are individuals with opioid use disorder, with a preference for

weekly or monthly injection, or those who frequently relapse with a history of non-adherence to oral treatment, and those with a history of overdose on methadone.

4.34. Members considered that the majority of new clients with opioid use disorder now initiate on buprenorphine with naloxone rather than methadone, however that the majority of individuals on methadone would be unlikely to switch treatment if buprenorphine depot were made available. Members considered that patient numbers were difficult to estimate, but considered that a significant minority of those taking sublingual buprenorphine with naloxone would switch to buprenorphine depot plus approximately 10% of methadone users, with total patient numbers likely to be over 1,000. Members considered that the uptake trend of antipsychotic depots could be used to model uptake of buprenorphine depot.

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

Population	Individuals with opioid use disorder currently undergoing opioid substitution treatment
Intervention	Buprenorphine depot subcutaneous (SC) injection (Buvidal) administered weekly or monthly, formulations: - 8 mg SC injection (weekly) -16 mg SC injection (weekly) -24 mg SC injection (weekly) -32 mg SC injection (weekly) -64 mg SC injection (monthly) -96 mg SC injection (monthly) -128 mg SC injection (monthly)
Comparator(s)	Buprenorphine/naloxone 8 mg/2 mg and 2 mg/0.5 mg tablets Average buprenorphine with naloxone daily dose estimated to be 18.34 mg to 19.6 mg Methadone 2 mg/ml, 5 mg/ml and 10 mg/ml formulations Average daily dose of 80 mg
Outcome(s)	Days abstinent from opioid use Reduced frequency of dosing Reduced medication abuse or diversion Reduced mortality risk from substance abuse Improved quality of life Health sector savings

Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.

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

Population	Individuals with opioid use disorder currently undergoing opioid substitution treatment
Intervention	Buprenorphine modified-release subcutaneous injection (Sublocade) given monthly - 300 mg per month for the first two months -100 mg per month thereafter
Comparator(s)	Buprenorphine/naloxone 8 mg/2 mg and 2 mg/0.5 mg tablets Average buprenorphine with naloxone daily dose estimated to be 18.34 mg to 19.6 mg Methadone 2 mg/ml, 5 mg/ml and 10 mg/ml formulations Average daily dose of 80 mg
Outcome(s)	Days abstinent from opioid use Reduced frequency of dosing Reduced medication abuse or diversion Reduced opioid use Reduced mortality risk from substance abuse Improved quality of life Health sector savings
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

5. Lisdexamfetamine for ADHD

Application

5.1. The Subcommittee considered:

- a supplier application from Takeda New Zealand Limited for the use of lisdexamfetamine (Vyvanse) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults, adolescents and children aged 6 years and older
- a consumer application for lisdexamfetamine for the treatment of ADHD.

Recommendation

5.2. The Subcommittee **recommended** that lisdexamfetamine for ADHD be funded in the context of treatments in mental health only if **cost neutral** to the Concerta brand of methylphenidate extended-release, subject to the following Special Authority criteria:

LISDEXAMFETAMINE
Initial application only from a paediatrician, psychiatrist, medical practitioner on the recommendation of a paediatrician or psychiatrist (in writing) or nurse practitioner on the recommendation of a paediatrician or psychiatrist (in writing). Approvals valid for 24 months.
All of the following:
1. ADHD (Attention Deficit and Hyperactivity Disorder); and
2. Diagnosed according to DSM-V or ICD 11 criteria; and
3. Any one of the following:
   3.1. Patient is taking a currently subsidised formulation of atomoxetine or methylphenidate hydrochloride (extended-release) which has not been effective or not tolerated; or
   3.2. Patient is taking a currently subsidised formulation of dexamfetamine sulfate (immediate-release) which has not been effective due to significant administration and/or compliance difficulties; or
   3.3. There is significant concern regarding the risk of diversion or abuse of immediate-release dexamfetamine sulfate; and
4. Lisdexamfetamine not to be used in combination with another stimulant or atomoxetine.

Renewal only from a paediatrician, psychiatrist, medical practitioner on the recommendation of a paediatrician or psychiatrist (in writing) or nurse practitioner on the recommendation of a paediatrician or psychiatrist (in writing). Approvals valid for 24 months.
Both:
1. The treatment remains appropriate and the patient is benefiting from treatment; and
2. Either:
   2.1. Applicant is a paediatrician or psychiatrist; or
   2.2. Applicant is a medical practitioner or nurse practitioner and confirms that a paediatrician or psychiatrist has been consulted within the last 2 years and has recommended treatment for the patient in writing

5.2.1. In making this recommendation, the Subcommittee considered:

- the health needs of children, adolescents and adults with ADHD, their families/whānau and wider society
- that the evidence was for short-term outcomes with lisdexamfetamine, rather than long-term clinical benefits
- evidence of benefit, with similar efficacy to methylphenidate
- the importance of holistic treatment of ADHD including non-pharmaceutical interventions and the risk that funding another stimulant may increase the overall pool of stimulant use and contribute to diversion in New Zealand.

Discussion

5.3. The Subcommittee noted that ADHD is one of the most common neuro-behavioural disorders occurring in children and adolescents with prevalence of 2.2% in New Zealand, greater prevalence in Māori of 3%, and affecting more boys than girls (New Zealand Health Survey 2018/19). The Subcommittee noted that ADHD is associated with lower socioeconomic status and that it affects an individual's schooling, employment and earning potential. The Subcommittee noted that ADHD is associated with an increased mortality rate and significant comorbidity eg increased risk of car accidents, anxiety/mood disorders, other neurodevelopmental disorders, obesity, substance use disorders, smoking and eating disorders. The Subcommittee noted that ADHD affects an individual's interpersonal relationships and parent or caregiver emotional health.

5.4. The Subcommittee noted that ADHD is complex and that the differential diagnosis can include complicated life experiences and trauma, which may also coexist with

ADHD. The Subcommittee considered that holistic treatment of ADHD including adjunctive non-pharmaceutical interventions (eg working with children at home and in educational settings) was important, although recognised the usefulness of pharmaceutical treatment especially for young children and where non-pharmaceutical behavioural interventions are not accessible. The Subcommittee considered that there was a risk of overdiagnosis and overtreatment especially where non-pharmaceutical interventions or approaches are inaccessible. The Subcommittee considered that it was important to safely diagnose and treat people with ADHD (particularly in primary care) by using, for example, thorough diagnostic assessments, alcohol and drug screening, non-pharmaceutical interventions, and appropriate attention to other individual factors.

5.5. The Subcommittee noted that two stimulants are available in New Zealand for the treatment of ADHD subject to Special Authority criteria: dexamfetamine, which is short acting and requires multiple daily dosing, and methylphenidate, which is funded in various forms including immediate-release and long-acting formulations. The Subcommittee noted that atomoxetine is the only open-listed treatment for ADHD and does not require prescription by a specialist. The Subcommittee noted that other treatments may be used to treat features of ADHD such as clonidine for young children with concomitant tic disorder, and bupropion, although these are not usually used as first-line treatments.

5.6. The Subcommittee noted that the supplier's treatment paradigm focused on the main pharmaceutical treatments for ADHD, however, the Subcommittee considered that non-pharmaceutical interventions were an important part of the treatment approach and appeared to be missing. The Subcommittee considered that a stimulant, generally methylphenidate, would be used as the first-line pharmacological treatment prior to atomoxetine for children and adolescents; while amphetamines may be used as first-line treatment in adults. The Subcommittee considered that the chosen sequence of treatments was dependent on the treatment's magnitude of benefit and other factors including risk of diversion, parental concerns about stimulants, the individual's ability to take pills, and the pharmaceutical's side effect profile especially for children with low weight or growth issues, comorbid tic disorder etc. The Subcommittee considered that about 70% of people with ADHD will respond to a first-line pharmaceutical and that those who switch may respond to a subsequent pharmaceutical treatment, with about 91% responding overall (Hodgkins et al. Eur Child Adolesc Psychiatry. 2012;21:477–92).

5.7. The Subcommittee noted that long-acting formulations are useful for older children, providing effect late in the day into the evening. The Committee considered that the lack of a funded long-acting dexamfetamine formulation may contribute to the preference for methylphenidate, although acknowledged that extended-release methylphenidate is currently restricted to where there are significant administration and/or compliance difficulties, or significant concern regarding the risk of diversion or abuse of immediate-release methylphenidate hydrochloride. However, the Subcommittee noted that the relative unavailability of specialists who can prescribe and issue Special Authority applications for stimulants can limit the ability to prescribe stimulants in primary care and members noted that many young adults are commencing treatment with atomoxetine instead of methylphenidate due to these challenges accessing specialist prescribers.

5.8. The Subcommittee considered that the risk of diversion (ie transfer of a controlled substance from the individual it was prescribed for to another for illicit use) with stimulants was significant, particularly given the imprecise diagnosis of ADHD. The

Subcommittee considered that compared with short-acting treatments, long-acting treatments may reduce the risk of diversion. The Committee also considered that the use of non-stimulant treatments and non-pharmaceutical interventions would help further, but that these approaches wouldn't eliminate diversion in this setting.

5.9. The Subcommittee noted that lisdexamfetamine is a long-acting pharmacologically inactive prodrug of dexamphetamine, which is a central nervous system stimulant, and that it is converted into its active form over a period of about 12 hours. The Subcommittee noted that lisdexamfetamine is classified as a Controlled Drug Class B1. The Subcommittee noted that Medsafe approved lisdexamfetamine for the treatment of ADHD in adults, adolescents, and children aged six years and older, and that lisdexamfetamine is available as a 30 mg, 50 mg, or 70 mg capsule taken orally once daily, titrated up to a maximum dose of 70 mg per day.

5.10. The Subcommittee noted that the supplier provided a substantial amount of evidence for the use of lisdexamfetamine in children, adolescents and adults with ADHD, consisting of randomised controlled trials, systematic reviews and meta-analyses, and cohort studies.

5.11. The Subcommittee noted the following evidence for lisdexamfetamine compared with atomoxetine for the treatment of ADHD in children and adolescents:

- Dittmann et al. CNS Drugs. 2013;27:1081-92
- Dittmann et al. CNS Drugs. 2014;28:1059-69
- Nagy et al. Eur Child Adolesc Psychiatry. 2016;25:141-9

5.12. The Subcommittee noted the following for lisdexamfetamine compared with methylphenidate for the treatment of ADHD in children and adolescents:

- Coghill et al. Eur Neuropsychopharmacol. 2013;23:1208-18
- Newcorn et al. CNS Drugs. 2017;31:999-1014

5.13. The Subcommittee noted evidence for lisdexamfetamine compared with mixed amphetamine salts in adults with ADHD:

- Adler et al. Postgrad Med. 2014;126:17-24
- Martin et al. Clin Drug Investig. 2014; 34: 147–157

5.14. The Subcommittee noted the following long-term (duration of 52 weeks or more) follow-up cohort studies including children, adolescents and adults with ADHD who received lisdexamfetamine:

- Coghill et al. CNS Drugs. 2017;31:625-38
- Joseph et al. Patient Prefer Adherence. 2016; 10: 391–405
- Findling et al. J Child Adolesc Psychopharmacol. 2013;23:11-21
- Setyawan et al. J Med Econ. 2013;16:1203-15
- Setyawan et al. J Med Econ. 2013;16:1275-89
- Weisler et al. CNS Spectr. 2009;14:573-85
- Findling et al. CNS Spectr. 2008;13:614-20

5.15. The Subcommittee noted that the available evidence reported an improvement in short-term functional outcomes with lisdexamfetamine and few studies reported long-term clinical benefits for the individual or their family/whānau. However, the Subcommittee considered that effective treatment of ADHD can reduce long-term disorders, accidents and substance abuse, and can help to improve the success of non-pharmaceutical interventions. The Subcommittee noted the heavy pharmaceutical industry influence on the evidence base and treatment paradigm for ADHD in general. However, the Committee considered that the wide body of evidence including randomised controlled trials, network meta-analyses, and cohort studies supported the efficacy of lisdexamfetamine as being similar to that of methylphenidate. The Subcommittee noted that lisdexamfetamine was reported to have greater efficacy than atomoxetine (as is reported with other stimulants).

5.16. The Subcommittee considered that lisdexamfetamine was not as well tolerated as methylphenidate and other funded ADHD medicines, especially in children and adolescents, but considered that its side effect profile was overall similar to that of other stimulants. The Subcommittee noted that evidence from database studies reported less discontinuation of lisdexamfetamine and less augmentation with lisdexamfetamine, compared with methylphenidate.

5.17. The Subcommittee considered that lisdexamfetamine would be an effective alternative stimulant option to methylphenidate and that it would be a reasonable option where methylphenidate is not sufficiently effective, as it would provide a longer-acting effective treatment option compared with other options such as atomoxetine. The Subcommittee considered that the greatest benefit from lisdexamfetamine would be in patients for whom methylphenidate was ineffective and who would benefit from dexamfetamine if not for the challenges of multiple daily dosing.

5.18. The Subcommittee considered that there were some reports of combination treatment of lisdexamfetamine with methylphenidate extended-release or long-acting but that there was insufficient evidence to determine whether this was safe or effective at this time. The Subcommittee considered that lisdexamfetamine should be used as part of a treatment paradigm including non-pharmaceutical, psychosocial interventions, but not in combination with another stimulant or atomoxetine. The Subcommittee noted that some people with ADHD also require treatments for adverse effects of stimulants.

5.19. The Subcommittee considered that the abuse potential of lisdexamfetamine as a stimulant would be less than that of dexamfetamine and, if funded, may be associated with a reduction in use of dexamfetamine. The Subcommittee

considered that funding lisdexamfetamine could increase the total pool of stimulant use overall in New Zealand and that increasing the number of pharmaceutical treatments available for ADHD could exacerbate the preference to treat the condition with medicines alone as opposed to a more holistic approach including adjunctive non-pharmaceutical treatments.

5.20. The Subcommittee considered that funding lisdexamfetamine would have the potential to grow the market, if this is preferable to treatment with methylphenidate. Although it was considered that uptake would more likely come from the majority of people taking dexamfetamine who would switch to once-daily lisdexamfetamine. The Subcommittee considered that as lisdexamfetamine is more effective than atomoxetine, patients on methylphenidate would switch to lisdexamfetamine instead of atomoxetine. However, the Subcommittee considered that patients who were well-established on a treatment would be less likely to switch.

5.21. The Subcommittee considered that it was appropriate to compare lisdexamfetamine with methylphenidate extended-release (Concerta) and that this was a more appropriate comparator than methylphenidate long-acting (Ritalin LA) due to the release profile.

5.33. The Subcommittee considered that lisdexamfetamine would be easy to use, that the capsule formulation would have advantages over tablets for those with difficulty swallowing pills, and that once-daily dosing would be more easily administered in schools than multiple daily dosing (eg with dexamfetamine). The Subcommittee noted that a benefit of a long-acting stimulant is that this provides an alternative to short-acting treatments, however, noted that several long-acting methylphenidate formulations are currently funded (although with additional funding restrictions above those of immediate-release formulations).

5.34. The Subcommittee considered that lisdexamfetamine would be appropriate as a second-line or third-line treatment for ADHD. The Subcommittee considered that use of lisdexamfetamine following an unsuccessful trial of either methylphenidate or atomoxetine would be appropriate, however, it would not be reasonable to use lisdexamfetamine where dexamfetamine has not been effective (unless due to issues with adherence to its dosing schedule). The Committee considered that the use of lisdexamfetamine would be appropriate in cases where there are concerns about diversion or immediate-release dexamfetamine adherence or administration difficulties. The Subcommittee considered that the Special Authority criteria for lisdexamfetamine should align with the current diagnostic criteria (DSM-5/ ICD 11) for accuracy, although members noted that these versions have less restrictive diagnosis of ADHD than DSM-IV and ICD 10.

5.35. The Subcommittee noted that challenges with accessing specialist prescribers for initial prescriptions and renewal would occur with lisdexamfetamine, if it were funded, and considered that it would also impact on primary care for diagnosis and management of ADHD. The Subcommittee considered that if lisdexamfetamine were funded, use of atomoxetine (which does not require prescription by a specialist) in the young adult population with moderate to severe ADHD would continue to increase, as is already occurring due to challenges accessing prescribers of stimulants.

5.36. The Subcommittee considered that, as a large proportion of people with ongoing mental health conditions like ADHD are managed by primary care without secondary care support, primary care services would benefit from implementation support and education regarding the management of patients with ADHD

irrespective of whether lisdexamfetamine were funded or not. Members considered that such education and support could include practical advice regarding assessment, criteria for referral to secondary care and non-stimulant management options (eg coaching, behavioural interventions, other pharmaceutical treatments).

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

Population	Patients aged over six years diagnosed with ADHD on currently funded regimens (eg methylphenidate ER, dexamfetamine, or atomoxetine) which are: • not effective or tolerated; or • not effective due to significant administration and/or compliance difficulties; or • associated with significant concern of risk of diversion or abuse (eg dexamfetamine).
Intervention	Lisdexamfetamine taken once daily, starting at 30 mg and titrated up to a maximum of 70 mg daily. Average daily dose in patients aged less than 18 years of age – 44.2 mg Average daily dose in patients aged over 18 years of age – 60.3 mg
Comparator(s) (NZ context)	Relevant currently funded agents at recommended dosages: • Dexamfetamine • Atomoxetine • Methylphenidate extended-release
Outcome(s)	Improved management of ADHD Improved compliance and adherence to relevant ADHD therapy Reduced risk of abuse and diversion of relevant ADHD medications
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	