Mental Subcommittee of PTAC
Meeting held 15 July 2013

(minutes for web publishing)

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Note that this document is not necessarily a complete record of the Mental Health Subcommittee meeting; only the relevant portions of the minutes 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.

These Subcommittee minutes were reviewed by PTAC at its meeting on 7 & 8 November 2013, the record of which will be available in January 2014.

Record of the Mental Health Subcommittee of PTAC meeting held at PHARMAC on 15 July 2013

1 Correspondence/Matters Arising

Paliperidone depot injection (Invega Sustenna)

1.1 The Subcommittee reviewed correspondence and information from clinicians and the supplier (Janssen) in support of paliperidone depot injection (Invega Sustenna), as well as the relevant minutes from previous PTAC and Mental Health Subcommittee meetings in relation to paliperidone depot injection. The Subcommittee noted that PTAC had recommended funding paliperidone depot injection only if it was cost-neutral versus risperidone depot injection.

1.2 The Subcommittee again noted that paliperidone is the active metabolite of risperidone, which is funded.

1.3 The Subcommittee considered that the availability of paliperidone depot injection would be unlikely to make any significant difference to the number of nurse visits as most patients would still need to be seen frequently.

1.4 The Subcommittee considered that there was no evidence to suggest that paliperidone depot injection would reduce hospital stays, noting that hospitalisation of patients and length of stay was complex and multifactorial and would be unlikely to be significantly affected by subtle differences in medicine administration. The Subcommittee noted that there was no evidence of a reduction in hospital stay in the clinical trials.

1.5 The Subcommittee noted that the clinical trial population is likely to be different from the population of patients who use antipsychotic depot injections in New Zealand, and reiterated its previous view that higher doses of paliperidone would be likely to be used in clinical practice.

1.6 The Subcommittee noted the claim that paliperidone depot injection would not require any oral supplementation during the first weeks of treatment. Members considered that this was unlikely to be the case in practice and that it was likely that oral supplementation would frequently be utilised.

1.7 Members noted that they were aware of possible conflicts of interest for some of the clinicians who had provided information in support of paliperidone depot injection and the Subcommittee considered that enquiries regarding potential conflicts of interest should routinely be sought from clinicians who make submissions to PHARMAC.

1.8 The Subcommittee noted a recent antipsychotic meta-analysis by Leucht et al (Lancet 2013;doi:pii: S0140-6736(13)60733-3) which showed that the side effects for oral risperidone and oral paliperidone were generally similar (with the exception of effects on QTc prolongation, which tended to favour paliperidone but which can be monitored in patients taking risperidone) and that this was likely to be the same for the depot presentations.

1.9 The Subcommittee considered that patients would probably prefer paliperidone depot injection as it is monthly, not fortnightly. The Subcommittee considered that paliperidone depot might be easier for clinicians to titrate. The

Subcommittee noted that these factors would be unlikely to translate into a significant clinical benefit over risperidone depot injection.

1.10 The Subcommittee considered that, although many clinicians would like to have access to paliperidone depot injection, it was unlikely that patients requiring a depot antipsychotic injection would be unable to access adequate treatment due to the lack of availability of paliperidone depot injection.

1.11 The Subcommittee reiterated its previous medium priority **recommendation** for paliperidone depot injection in the context of the mental health therapeutic area on the basis that patients would prefer it and it might be more convenient to use.

2 Asenapine

2.1 The Subcommittee reviewed the May 2012 funding application from Lundbeck for asenapine (Saphris) 5 mg and 10 mg orodispersible tablets for the treatment of bipolar 1 disorder and schizophrenia, the relevant minutes from PTAC's review of the application in August 2012, and additional information subsequently provided by the supplier.

2.2 The Subcommittee noted that PTAC had recommended that asenapine is funded for bipolar 1 disorder only if it is cost-neutral to aripiprazole and ziprasidone taking into account future generic pricing and that the application should be referred to the Mental Health Subcommittee for advice on appropriate Special Authority criteria. The Subcommittee noted that PTAC had recommended that the application for asenapine in schizophrenia be declined.

2.3 The Subcommittee reviewed reports of several clinical trials involving the use of asenapine in schizophrenia: Potkin et al (J Clin Psychiatry 2007;68(10):1492-500), the clinical trial report (CTR) summary of 041021 (unpublished), CTR 041022 (unpublished), CTR 041512 (unpublished), Buchanan et al (J Clin Psychopharmacol 2012;32(1):36-45), Schoemaker et al (Pharmacopsychiatry 2010;43:138-46), study A7501012 (no CTR, unpublished) and study A041023 (unpublished, information taken from the Medsafe datasheet).

2.4 The Subcommittee considered that studies were of moderate quality but the strength of the evidence for asenapine in schizophrenia was weak and showed that asenapine was only marginally more effective than placebo and generally less effective than olanzapine. The Subcommittee expressed its concern over the non-publication of key clinical trials provided in the submission.

2.5 The Subcommittee noted that the supplier considered that the studies in schizophrenia supported the non-inferiority of asenapine to olanzapine because the differences between the two treatments in terms of the PANSS scores at 26 weeks and 52 weeks were "clinically insignificant." The Subcommittee agreed with PTAC's view that olanzapine was more effective than asenapine in the treatment of schizophrenia the clinical trials.

2.6 The Subcommittee reviewed reports of several clinical trials involving the use of asenapine in bipolar 1 disorder: McIntyre et al (Bipolar Disord 2009;11:673-86); McIntyre et al (Bipolar Disord 2009;11:815-26); McIntyre et al (J Affect Disord 2010;122:27-38); McIntyre et al (J Affect Disord 2010;126(3):358-65) and Szegedi et al (J Clin Psychopharmacol 2012;32(1):46-55). The Committee considered that the studies were of good quality and provided moderate

support for the effectiveness of asenapine versus placebo in the treatment of bipolar 1 disorder.

2.7 The committee considered that the studies did not definitively support the non-inferiority of asenapine to olanzapine in bipolar 1 disorder, noting that olanzapine was more effective than asenapine on some measures. The Subcommittee noted that the post-hoc analyses referred to by the supplier in support of its claim that asenapine is non-inferior to olanzapine were exploratory and, therefore, it would not be appropriate to draw such a conclusion from the analyses. However, the Subcommittee considered that the clinical benefit from asenapine was likely to be similar to other antipsychotics for bipolar 1 disorder. The Subcommittee noted a meta-analysis by Yildiz et al (Neuropsychopharmacology 2011;36(2):375-89) showing that antipsychotics (including asenapine) had a faster onset of action and were more effective than mood stabilisers in bipolar 1 disorder.

2.8 The Subcommittee noted that in recent years there has been a shift to using antipsychotics, rather than mood stabilisers, as first-line treatment for bipolar 1 disorder in the acute setting and that it was now reasonably common for antipsychotics to be continued as monotherapy for maintenance treatment.

2.9 The Subcommittee noted PTAC's concern regarding the potential for 'dose-creep'. The Subcommittee considered this was a valid concern, noting that the supplier's submission stated that the average daily dose in Australia in December 2011 was 11.7 mg and in February 2012 it was 15.0 mg. Further, the Subcommittee considered that it was possible that clinicians would increase the dose to improve efficacy, given that it appeared that asenapine was not as effective as olanzapine at 10 mg daily.

2.10 The Subcommittee noted that asenapine must be taken sublingually twice daily and that the patient should not eat or drink within 10 minutes of administration. The Subcommittee considered that compliance could be a significant issue with asenapine, which would likely mean that asenapine would be less efficacious in the 'real world' setting than in clinical trials where patients are more closely monitored and are more likely to take the medication properly.

2.11 The Subcommittee considered that asenapine appeared to offer little benefit over existing treatment options for bipolar 1 disorder, with the possible exception of patients who experience significant weight gain from existing options – although the Subcommittee noted that weight gain is also a side effect of asenapine.

2.12 The Subcommittee **recommended** that asenapine be funded for bipolar 1 disorder only if it was cost-neutral to the currently funded antipsychotics, taking into account future generic pricing for ziprasidone and aripiprazole. The Subcommittee considered that there was no reason to fund asenapine for schizophrenia given the lack of evidence of effectiveness; however, members considered it would be impractical to limit funding to bipolar 1 disorder and, therefore, **recommended** that if asenapine was funded for bipolar 1 disorder it should also be funded for schizophrenia.

3 Naltrexone

3.1 The Subcommittee noted that naltrexone is registered for use within a comprehensive treatment programme for alcohol dependence and as adjunctive therapy in the maintenance of formerly opioid-dependent patients

who have ceased the use of opioids such as heroin or morphine. The Subcommittee noted that naltrexone is currently funded via Special Authority for patients enrolled in a recognised comprehensive treatment programme for alcohol dependence and where the applicant works in or with a Community Alcohol and Drug Service (CADS).

3.2 The Subcommittee noted that PHARMAC has received requests to widen access to naltrexone for a variety of uses/reasons. The Subcommittee reviewed the information provided by applicants and PHARMAC staff in relation to these requests, as well as some additional potential uses identified by PHARMAC staff.

3.3 The Subcommittee noted that a decision had recently been made to increase the approval periods for the existing Special Authority initial and renewal applications from 3 to 6 months, which will allow high-needs patients to receive funded naltrexone for more than 6 months in a 12-month period.

3.4 The Subcommittee noted that Nurse Prescribers working within CADS currently cannot make Special Authority applications as these are restricted to medical practitioners (as defined in the Pharmaceutical Schedule). The Subcommittee considered that it would be reasonable for a Nurse Prescriber who is legally entitled to prescribe naltrexone and who works within a CADS to be able to make Special Authority applications if the patient otherwise meets the criteria and, therefore, **recommended** that the form be changed to allow applications from "any relevant practitioner" rather than "any medical practitioner."

3.5 The Subcommittee noted that PHARMAC had received a request from a private psychiatrist to be able to make naltrexone Special Authority applications despite not working in or with a CADS. Members considered that from the information provided it was not clear how the services offered to the patient differ from services offered by CADS, so it was not possible to ascertain whether or not these could be considered a "recognised comprehensive treatment programme for alcohol dependence." It was also not clear from the information provided whether the services offered would be sufficient to meet the accreditation standards outlined in the second criterion. The Subcommittee suggested that PHARMAC staff seek more information from the psychiatrist around these points. Members noted that it might be possible for the psychiatrist to seek accreditation. The Subcommittee noted that clinical trial evidence suggested that naltrexone was more effective when used as part of a comprehensive treatment programme, which is why the funding is restricted in this way.

3.6 The Subcommittee considered that there appeared to be little to no good-quality evidence in support of the use of naltrexone in opioid dependence, rapid opioid detoxification, depersonalisation disorder, or any of the potential uses of low-dose naltrexone (including HIV/AIDs, various cancers, autoimmune diseases and central nervous system disorders).

3.7 The Subcommittee noted that naltrexone was available on the HML for use in the treatment of opioid-induced constipation. However, the Subcommittee noted that although there appears to be some evidence for the use of methylnaltrexone for this indication, there appears to be little to no evidence for the use of naltrexone for opioid-induced constipation. The Subcommittee **recommended** that this issue be brought to the Gastrointestinal Subcommittee for discussion.

3.8 The Subcommittee considered that there may be some evidence for the use of naltrexone for treatment-resistant cholestasis, and **recommended** that this should be taken to the Gastrointestinal Subcommittee for review.

3.9 The Subcommittee noted that PHARMAC had received requests to remove the Special Authority from naltrexone altogether. However, the Subcommittee considered that there was a large financial risk of off-label use of naltrexone, including in several indications for which there is no good evidence of benefit, and therefore **recommended** that the Special Authority not be removed at this time.

4 Buprenorphine sublingual tablets (Subutex)

Introduction

4.1 The Subcommittee reviewed information from PHARMAC staff, the supplier (Reckitt Benckiser), the Waitemata Community Alcohol and Drugs Service (CADS), the National Association of Opioid Treatment Providers (NAOTP) and individual clinicians in relation to requests for funding of buprenorphine sublingual tablets (Subutex) for use in women who are stabilised on buprenorphine with naloxone (Suboxone) and become pregnant and/or are breast feeding, and for patients eligible for Suboxone funding who are allergic to naloxone.

4.2 The Subcommittee noted that Subutex is not registered for use in New Zealand [Withheld under s 9(b)(ii) of the OIA (commercial prejudice)].

4.3 The Subcommittee noted that opiate-dependent women experience a six-fold increase in maternal obstetric complications such as low birth weight, toxaemia, third-trimester bleeding, malpresentation, puerperal morbidity, foetal distress and meconium aspiration. Neonatal complications include narcotic withdrawal, postnatal growth deficiency, microcephaly, neurobehavioural problems, increased neonatal mortality and a 74-fold increase in sudden infant death syndrome. (Minozzi et al. Cochrane Database Syst Rev. 2008; 16;(2):CD006318).

4.4 The Subcommittee noted that the currently funded options for opiate-dependent pregnant or breastfeeding women are methadone or Suboxone (the latter funded only for patients who meet the Special Authority criteria). The Subcommittee noted that the key reason for the naloxone component of Suboxone is to reduce the risk of abuse and diversion of buprenorphine and that naloxone has no therapeutic benefit in the treatment of opioid addiction.

4.5 The Subcommittee noted that Suboxone is contraindicated in pregnant women and breastfeeding women in New Zealand (it is classified as pregnancy Category C), with the cautions in pregnancy and breastfeeding in the datasheet referring to the buprenorphine component, and that both Suboxone and Subutex are contraindicated in pregnancy and breastfeeding in Australia. The Subcommittee noted a communication from Medsafe to PHARMAC noting that Suboxone is not contraindicated in pregnancy in the United States and Europe and that the risks in pregnancy and breastfeeding are thought to be similar for both Suboxone and Subutex.

4.6 The Subcommittee noted that neither naloxone nor methadone is contraindicated for use in pregnancy in New Zealand, although the Medsafe datasheets for both agents contain warnings about their use in pregnancy and breastfeeding.

4.7 The Subcommittee noted that, internationally, methadone is currently the treatment of choice for the majority of opioid-dependent women who become pregnant.

Review of evidence

4.8 The Subcommittee noted that there was evidence of reproductive toxicity from buprenorphine in animal models with reduced implantation and live births, poorer weight gain and survival, and developmental delay (US FDA datasheet). There appeared to be no evidence of teratogenesis in the period of organogenesis in animal models.

4.9 The Subcommittee noted that animal studies of buprenorphine with naloxone administered in the period from late gestation to weaning showed similar findings, with reproductive toxicity but no evidence of teratogenicity (Medsafe datasheet). Animal studies with naloxone alone at up to 1,000 times higher than human doses revealed no reproductive toxicity or teratogenesis (Medsafe datasheet). The Subcommittee noted that there was only one report of a congenital anomaly (not specified) for naloxone in the US FDA database of adverse drug reactions, and there were scattered reports of congenital abnormalities from buprenorphine in the FDA postmarketing surveillance data.

4.10 The Subcommittee noted that there was evidence of teratogenicity from high doses of methadone in animal studies in some species but not others. A 2010 review of TERIS (Teratogen Information System, and online database) referenced in the FDA datasheet found that there was 'limited to fair' evidence that methadone did not pose a substantial teratogenic risk. The Subcommittee noted that the FDA database of adverse drug reactions shows increased reporting rates of congenital eye disorder associated with methadone in pregnancy, but there was no significant reporting of any other congenital abnormalities. The Subcommittee noted that there are conflicting reports of increased rates of sudden infant death syndrome associated with methadone. The Subcommittee noted that infants born to women receiving methadone have an increased incidence of reduced foetal growth from which they later recover, and mild deficits in psychometric and behavioural tests. A retrospective study of 101 women transferred from opiates to methadone in pregnancy found no increased rate of miscarriage in the second trimester or premature delivery (Luty et al. J Subst Abuse Treat. 2003 Jun;24(4):363-7).

4.11 The Subcommittee noted the publication of a double-blind, randomised, placebo controlled trial comparing the use of methadone and buprenorphine initiated in 175 opioid-dependent pregnant women (Jones et al. N Engl J Med 2010;363:2320-31). The study found no significant differences in total neonatal abstinence syndrome (NAS) score, peak NAS score, the percentage of neonates requiring NAS treatment, or head circumference. Neonates exposed to buprenorphine required significantly less morphine than those exposed to methadone, spent an average of 43% less time in hospital, and had a significantly shorter duration of NAS treatment. There was no significant difference in serious or non-serious neonatal adverse events. There was a higher rate of non-serious maternal adverse events in the methadone group, particularly non-serious cardiovascular events (p=0.01). There were no between-group differences in either maternal or fetal serious adverse event, or

in foetal nonserious adverse events. There were no reports of congenital abnormalities or miscarriages in either group.

4.12 The Subcommittee considered that there were some limitations with the Jones et al (2010) study described above. The reported results were from a per-protocol analysis not an intention to treat (ITT) analysis, which is potentially significant given that the discontinuation rate was significantly higher in the buprenorphine arm (33% versus 18% in the methadone arm). Further, data on the demographic characteristics of the ITT population is not presented and it appears possible from the data that is presented that there may have been some relevant differences between the two study arms in terms of cumulative duration of substance abuse.

4.13 The Subcommittee noted that a Cochrane review of trials prior to the publication of the Jones et al (2010) study found no significant difference in mother or child outcomes between buprenorphine and methadone (Minozzi et al. Cochrane Database Syst Rev. 2008;16;(2):CD006318). The authors noted that the trials identified were too few and the sample size too small to make a definitive conclusion about the superiority of one treatment over the other.

4.14 The Subcommittee noted that it is not known whether naloxone is excreted in breast milk and that there is no data on safety in breastfeeding and for infants of breastfeeding mothers, although it is indicated for use in infants in New Zealand.

4.15 The Subcommittee noted that the Medsafe datasheet for methadone records the amount excreted into breast milk as minute and unlikely to harm the foetus.

4.16 The Subcommittee considered that it was difficult to ascertain the rate of allergy (anaphylactic reaction) to naloxone but it was likely to be very low.

General discussion and recommendations

4.17 The Subcommittee noted that the main issue around safety of the various treatment options appears to be more one of lack of human studies rather than evidence of harm.

4.18 The Subcommittee considered that the available human data, including post-marketing pharmacovigilance data, suggests that there is no strong evidence for any safety concern with naloxone and that the risk of harm from buprenorphine appears similar to that of methadone.

4.19 The Subcommittee considered that there is no strong evidence supporting an increased risk of miscarriage in patients transferred between buprenorphine-based treatment and methadone.

4.20 The Subcommittee considered that, notwithstanding the limitations in the results analyses, data from the Jones et al (2010) study discussed above suggests that there may be an advantage of buprenorphine over methadone on some neonatal outcome measures; however, the study investigated *initiation* of these treatments in opioid-dependent pregnant women, which is different from the situation for which buprenorphine funding is being sought. The Subcommittee noted that the study had a very high dropout rate in the buprenorphine arm, which could lead to adverse outcomes if it also occurred in a 'real world' setting (which is more likely given how closely patients are monitored in clinical trials).

4.21 The Subcommittee considered that there was a high risk of diversion and, therefore, treatment discontinuation, if buprenorphine without naloxone was made available to pregnant women undergoing opioid substitution treatment.

4.22 The Subcommittee expressed concern that, if funded as requested, there was a risk that Subutex would be prescribed 'prophylactically' for patients who state they are planning to become pregnant, which could increase the risk of abuse and diversion and discontinuation.

4.23 The Subcommittee noted that although the average time to breastfeed babies in New Zealand was six months or less it would be difficult to place a time limit on how long a patient could receive Subutex for given the large variation in duration of breastfeeding. The Subcommittee considered that there was a high risk this aspect of the funding could be open to abuse.

4.24 The Subcommittee expressed concern that the request was for funding of an unregistered medicine for an off-label use in a pregnancy-specific indication for a treatment with demonstrated reproductive toxicity in animals.

4.25 On balance, the Subcommittee considered that the evidence for using Subutex instead of Suboxone or methadone in pregnant or breastfeeding women is weak and does not outweigh the risk of abuse (relapse to intravenous opioid use), diversion and discontinuation from Subutex. Therefore, the Subcommittee **recommended** that the application to fund Subutex for women on Suboxone who become pregnant or are breastfeeding be declined.

4.26 The Subcommittee considered that there appeared to be no reason why patients with a demonstrated anaphylactic reaction to naloxone could not be maintained on, or transferred to, methadone. Therefore, the Subcommittee **recommended** that the application to fund Subutex for patients eligible for Suboxone who are allergic to naloxone be declined.

5 Methylphenidate for off-label indications

5.1 The Subcommittee noted that PHARMAC had received funding applications from clinicians for widening access to methylphenidate (all currently funded presentations) for use in treatment-resistant depression, depression in terminally ill patients, and apathy in patients with traumatic brain injury, all of which are off-label indications.

5.2 The Subcommittee noted that the applicants had provided no published evidence in support of the applications but that PHARMAC staff had provided some information from a rapid literature search.

5.3 The Subcommittee noted that methylphenidate is only registered for use in New Zealand for the treatment of attention deficit and hyperactivity disorder (ADHD) and narcolepsy.

5.4 The Subcommittee noted that under regulation 22 of the Misuse of Drugs Act 1977 methylphenidate can only be prescribed by a psychiatrist or paediatrician (for ADHD only), an internal medicine specialist (for narcolepsy only) or a palliative care specialist (for use in palliative care only), or by any other medical practitioner on the written recommendation of one of these specialists (only for the relevant condition as specified for each specialty).

5.5 As such, the Subcommittee noted that of the three requested indications, methylphenidate could only legally be prescribed for depression in terminally ill patients.

5.6 The Subcommittee noted that it was considering the applications in the context of the use of methylphenidate in the relevant indications in both the hospital and community markets.

Treatment-resistant depression

5.7 The Subcommittee noted that methylphenidate is included in international guidelines as an option for treatment-resistant depression.

5.8 The Subcommittee considered that there appeared to be little evidence in support of the use of methylphenidate in treatment-resistant depression. Members noted that recommendations on its use by psychiatry associations overseas appeared to be based on clinical consensus rather than evidence.

5.9 The Subcommittee noted results of a double-blind randomised controlled trial (Petkar et al. J Clin Psychopharmacol 2006;26:653-656) and a systematic review (Fleurence et al. Psychopharmacol Bull 2009;42:57-90) that found no evidence of clinical efficacy from methylphenidate in patients with treatment-resistant depression. The Subcommittee noted that a Cochrane review of psychostimulants for depression determined that few clinically relevant conclusions could be drawn from the available literature (Candy et al. Cochrane Database Syst Rev 2008;16(2):CD006722).

5.10 The Subcommittee considered that based on the doses used in clinical trials, it would be reasonable to assume that starting doses of between 20 mg and 30 mg (increasing to 50 mg in cases of partial response) would be used in clinical practice, as an add-on therapy. Members considered that the time on treatment could vary greatly between patients, ranging from weeks to years/indefinitely.

5.11 The Subcommittee noted that there was a large range of alternative funded treatment options for patients with treatment-resistant depression.

5.12 The Subcommittee considered that there was no niche use for methylphenidate in hospitalised patients with treatment-resistant depression compared with community-based patients.

5.13 The Subcommittee considered that the risk of abuse and diversion if methylphenidate was funded for treatment-resistant depression would be high.

5.14 The Subcommittee noted that it was likely that methylphenidate will be recommended for use in treatment-resistant depression in the new Royal Australian New Zealand College of Psychiatry (RANZCP) guidelines for the treatment of depression due to be published in May 2014.

5.15 The Subcommittee **deferred** making a recommendation in relation to methylphenidate for treatment-resistant depression pending publication of the new RANZCP guidelines for treatment of depression. .

Depression in terminally ill patients

5.16 The Subcommittee noted that a 2009 review of methylphenidate for depression, apathy and fatigue in ill and terminally ill adults considered that conflicting

results, small size, and poor methodologic quality of the clinical trials limit the ability to draw inferences regarding the efficacy of methylphenidate, although the evidence of its safety is stronger (Hardy et al. Am J Geriatr Pharmacother 2009;7:34-59). The authors concluded that the available evidence suggests possible effectiveness of methylphenidate for depressive symptoms, fatigue, apathy and cognitive slowing in various medically ill populations.

5.17 The Subcommittee noted the results of a small trial examining the effect of methylphenidate in 30 hospice patients which found that methylphenidate had positive effects on fatigue and depression (Kerr et al. J Pain Symptom Manage 2012;43:68-77).

5.18 The Subcommittee noted that palliative care was a difficult area to study and it was possible that no better evidence would be available in the near future.

5.19 The Subcommittee noted that some international guidelines for management of patients with advanced cancer recommend the use of methylphenidate at doses of 2.5–5 mg increasing every two days to a maximum of 20–30 mg per day.

5.20 The Subcommittee noted that one potential advantage of methylphenidate for this indication was a possible faster onset of therapeutic effect.

5.21 The Subcommittee considered that there was a large range of alternative funded treatments for depression, although there are potential issues of tolerability in terminally ill patients and some patients may not live long enough for antidepressants to take effect. The Subcommittee was unsure as to whether there was a significant unmet clinical need in this patient population that could be met by methylphenidate.

5.22 The Subcommittee noted that there was potential for undesired side effects from methylphenidate in this patient population, for example anorexia.

5.23 The Subcommittee considered that if access to methylphenidate was widened to include its use in palliative care it should continue to be subject to Special Authority and hospital restrictions. Members considered that it would be very difficult to define terminally ill in such a restriction, noting that the financial risk could be high if use was not appropriately restricted given the large numbers of people dying each year in New Zealand (around 200,000 per year). The Subcommittee considered that it would not be appropriate to restrict funding to in-hospice use because hospices manage the care of only a small proportion of dying people.

5.24 The Subcommittee noted that if access was widened to include palliative care there would be a high potential for abuse and diversion of methylphenidate, not necessarily by the patient.

5.25 The Subcommittee **recommended** that given the potential risks and poor evidence of clinical benefit the application should be declined.

5.26 The Subcommittee considered that if the applicants were able to provide further evidence of clinical benefit and provide a workable definition of a discrete patient group the application could be re-considered; however, if this were to occur the Subcommittee **recommended** that the application be taken to PTAC for a final recommendation.

<u>Traumatic brain injury</u>

5.27 The Subcommittee noted that there appeared to be little evidence in support of the use of methylphenidate to treat apathy in patients with traumatic brain injury (TBI).

5.28 However, the Subcommittee noted that there were a number of reports of clinical studies investigating the effect of methylphenidate on cognition and behaviour in patients with TBI which seemed to suggest that it has a positive effect on cognitive outcomes including memory, attention and concentration as well as behavioural outcomes such as aggression.

5.29 The Subcommittee noted that the doses used in patients with TBI appeared to be in the range of 20–60 mg per day.

5.30 The Subcommittee considered that there could be a place for methylphenidate in the treatment of patients with severe/serious brain injury; however, members considered that it could be difficult to place appropriate restrictions on the use of methylphenidate in such patients due to the difficulty in defining the patient group – for example, even TBI not associated with a loss of consciousness increases the risk of adverse cognitive and other outcomes.

5.31 The Subcommittee noted that, partly due to the potential difficulties defining the patient group and partly due to the high potential patient numbers (potentially around 20,000 people per year), there was a high risk of abuse and diversion as well as a high financial risk associated with the use of methylphenidate in this patient population.

5.32 The Subcommittee deferred making a recommendation in relation to the application, and instead **recommended** that PHARMAC staff seek advice from TBI experts (e.g. in the head injury unit at Burwood Hospital) and from the Neurological Subcommittee of PTAC and take the application to PTAC for a final recommendation. The Subcommittee noted that it appeared from the current legislation that methylphenidate cannot legally be prescribed for use in TBI at present (with the exception of palliative care for such patients).

6 Atomoxetine for patients with ADHD at high risk of psychosis

6.1 The Subcommittee noted that it had previously recommended that access to atomoxetine be widened to include patients with ADHD who are at high risk of psychosis from stimulants (i.e. dexamphetamine and methylphenidate) with a high priority. The Subcommittee noted that PHARMAC staff were seeking further information in relation to this recommendation.

6.2 The Subcommittee considered that the available evidence, principally consensus expert opinion, indicates that stimulants are a known psychotomimetic for individuals with schizophrenia, such that stimulants should not be used in patients with an Axis I disorder of schizophrenia, psychosis not otherwise specified or manic episode with psychosis (Greenhill et al. J Am Acad Child Adolesc Psychiatry 2002;41(2 Suppl):26S-49S).

6.3 The Subcommittee considered that it would be reasonable to assume that patients with ADHD who have a strong family history of psychosis may also be at increased risk of psychosis associated with stimulant use. The Subcommittee noted that clinical trials of stimulants for individuals with ADHD invariably exclude patients with psychosis so that systematic study of this population is non-existent.

6.4 The Subcommittee noted that patients with ADHD who developed psychosis while taking subsidised stimulants would meet the current access criteria for atomoxetine (criterion 3.1).

6.5 The Subcommittee **recommended** that access to atomoxetine be widened to include patients with ADHD with existing or previous psychoses and/or who have a first-degree relative with schizophrenia, with a high priority.

6.6 The Subcommittee considered that the number of additional atomoxetine patients if access was widened as recommended would be low, in the region of 100 patients per year.

7 Reboxetine for depression

7.1 The Subcommittee noted that during implementation of the HML, PHARMAC received queries about the use of reboxetine for depression and was now seeking the Subcommittee's advice on this matter.

7.2 The Subcommittee noted that reboxetine is a selective noradrenaline reuptake inhibitor (SNRI) indicated in New Zealand for the treatment of depression. Members noted that the usual dose in the treatment of depression would be approximately 8 mg per day.

7.3 The Subcommittee noted that the results of two large meta-analyses suggested that reboxetine was less effective and was less well tolerated than the selective serotonin reuptake inhibitor (SSRI) antidepressants (Eyding et al. BMJ 2010;341:c4737; Cipriani et al. Cochrane Database Systematic Review 2012;7:CD006534). The Subcommittee noted that the BMJ publication concluded that reboxetine is an ineffective and potentially harmful antidepressant, although members felt that the potential for harm was overstated in this review.

7.4 The Subcommittee considered that there was a large range of alternative treatment options for patients with depression and there did not appear to be any significant unmet clinical need that could be met by reboxetine. Members considered that it would be unlikely to be used much if it were funded.

7.5 The Subcommittee considered that while reboxetine did not appear to offer any clinical benefit compared with the funded alternatives, there was no clinical reason not to list it and, therefore, the Subcommittee **recommended** that reboxetine be funded without restrictions if it were cost neutral to the SSRI antidepressants.

8 SNRIs for pain management

8.1 The Subcommittee noted that during implementation of the HML, PHARMAC received queries about the use of SNRIs for pain management and was now seeking the Subcommittee's advice on this matter.

8.2 The Subcommittee noted that the queries appeared to relate to the use of serotonin noradrenaline reuptake inhibitors (duloxetine and venlafaxine) rather than selective noradrenaline reuptake inhibitors (reboxetine).

8.3 The Subcommittee considered that there appeared to be reasonably good evidence for the use of duloxetine in the treatment of painful diabetic neuropathy. The Subcommittee noted that duloxetine was registered for use in diabetic peripheral neuropathic pain in New Zealand, although PHARMAC has only received a funding application for duloxetine in depression (not currently under active consideration for funding).

8.4 The Subcommittee considered that based on its mechanism of action venlafaxine was likely to provide a similar benefit to duloxetine for neuropathic pain, although the evidence base was not as strong (fewer trials having been conducted).

8.5 The Subcommittee considered that the serotonin and noradrenaline effects of venlafaxine were more unbalanced than duloxetine so there was a possible theoretical pharmacological advantage from duloxetine in the management of neuropathic pain, but there was no clinical evidence to support this and members considered that it was unlikely any difference in efficacy would be great enough to support a price difference between the two agents in terms of consideration for funding.

8.6 The Subcommittee considered that the effect size for the SNRIs in neuropathic pain was likely similar to the tricyclic antidepressants. The Subcommittee noted that other potential treatments that were currently funded were tramadol and gabapentin.

8.7 The Subcommittee considered that there was an unmet clinical need for a different class of treatment for the management of neuropathic pain which could at least partly be met by the availability of an SNRI.

8.8 The Subcommittee considered that, if funded for neuropathic pain, SNRIs would likely be used in combination with gabapentin although there might be some displacement of gabapentin use.

8.9 The Subcommittee **recommended** that PHARMAC progress the listing of an SNRI antidepressant for use in neuropathic pain with a medium priority.

8.10 The Subcommittee noted that PHARMAC was currently progressing a proposal to remove the Special Authority restrictions from one of the funded brands of venlafaxine. The Subcommittee was supportive of this proposal and considered that this would adequately address the clinical need for an SNRI for neuropathic pain.