Mental Health Subcommittee of PTAC
Meeting held 8 June 2012

(minutes for web publishing)

Mental Health Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

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; and
- that parts of the minutes relating to hospital pharmaceuticals and the establishment of a national list of pharmaceuticals for use in DHB hospitals are included in a separate document along with the original Hospital Pharmaceuticals Subcommittee minutes and final recommendations made by PTAC in relation to pharmaceuticals in this therapeutic area.

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 8 & 9 November 2012.

1 Previous recommendations/action points

1.1 The Subcommittee noted the status update provided by PHARMAC staff in relation to recommendations/action points from Mental Health Subcommittee meetings of October 2006, October 2007, May 2008, July 2009 and June 2010.

1.2 The Subcommittee noted that it had previously **recommended** that quetiapine modified-release tablets be funded with low priority. The Subcommittee considered that this preparation of quetiapine still potentially has a place in therapy for patients who have problematic peak/trough effects from the immediate-release preparation at higher doses although there was no evidence to support this. However, the Subcommittee considered that it would not change its previous priority.

2 Correspondence/Matters Arising

2.1 The Subcommittee reviewed correspondence from Janssen-Cilag Pty Ltd in regards to the funding application for paliperidone palmitate depot injection (Invega Sustenna) for the treatment of schizophrenia, subject to the same Special Authority criteria as risperidone depot injection (Risperdal Consta). The Subcommittee noted that this was in response to PTAC's (August 2010) and this Subcommittee's (June 2010) recommendations for the product. The Subcommittee noted that PTAC had recommended that paliperidone depot injection only be funded if cost-neutral or cost-saving compared to risperidone depot injection and that this Subcommittee had recommended that it be funded with low priority.

2.2 The Subcommittee noted the information presented by the supplier and considered that no new clinical evidence had been presented. The Subcommittee considered that the monthly dose of 138mg used in PHARMAC's analysis was appropriate because the treatment population in New Zealand are likely to be more unwell when compared to the trial population. The Subcommittee also considered that risperidone depot injection can now be injected into both deltoid and gluteal sites.

2.3 The Subcommittee considered that it was reasonable to assume paliperidone depot injection was unlikely to result in less nurse visits due to less frequent administration, compared with risperidone depot injection.

2.4 The Subcommittee considered that paliperidone depot injection does have less potential drug-drug interactions when compared to risperidone depot injection and is useful in that respect. The Subcommittee considered that there is no clinical trial evidence that paliperidone depot injection enables patients to be discharged earlier from hospital but clinical experience suggests that this may be true. The Subcommittee considered that it would be appropriate to assume that paliperidone depot injection would result in a reduction of hospitalisation of 1 day per patient, on initiation of treatment, but this could be an overestimation. The Subcommittee considered that although these patients can be discharged earlier, they still need to be monitored closely in the initial stages for dose adjustments to determine the right maintenance dose.

2.5 The Subcommittee **recommended** that paliperidone depot injection be funded with medium priority in the context of the mental health therapeutic area, a change from its previous low priority.

2.6 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publically funded health and disability support services and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

3 Therapeutic group review

3.1 The Subcommittee noted the review of funded Mental Health pharmaceuticals provided by PHARMAC staff. The Subcommittee considered that if the Special Authority for mirtazepine is removed, few existing patients on selective serotonin reuptake inhibitors (SSRIs) or venlafaxine would switch. Depending on how it is marketed, the Subcommittee considered that some new patients could be initiated on mirtazepine instead of venlafaxine. The Subcommittee considered that about 20% of patients who would otherwise have been on venlafaxine, would be initiated on mirtazepine instead. The Subcommittee considered that a much smaller proportion of new patients would use mirtazepine instead of the SSRIs because of clinician familiarity with the SSRIs.

3.2 The Subcommittee noted that there are outstanding funding applications for venlafaxine immediate-release tablets and duloxetine. The Subcommittee noted that PHARMAC will not be pursuing the listing of these two treatments because it would be unlikely that funding of an immediate-release venlafaxine would achieve significant savings and the current proposed pricing for duloxetine is not cost neutral or a savings to the Pharmaceutical Budget when compared to mirtazapine (based on the Subcommittee's recommendations in July 2009).

3.3 The Subcommittee noted that reboxetine (Edronax), a noradrenaline reuptake inhibitor has been registered in New Zealand since 2000 but PHARMAC has not received a funding application. The Subcommittee considered that there was no particular clinical demand for it to be funded because clinical trial evidence suggests it is not very efficacious. The Subcommittee noted that trazodone, a serotonin antagonist and reuptake inhibitor is not yet registered in New Zealand. The Subcommittee considered that it could potentially have a small niche use in elderly patients.

3.4 The Subcommittee noted the increased use of quetiapine over the last few years. The Subcommittee considered that low doses were increasingly being used to treat insomnia, in middle-aged patients and as a long term treatment. The Subcommittee noted that it is also being promoted as an anxiolytic. The Subcommittee considered that it is difficult to stop treatment after it is initiated and abuse is a problem.

3.5 The Subcommittee noted that aripiprazole is funded subject to Special Authority restriction for patients with schizophrenia or related psychoses. The Subcommittee reviewed two clinical studies forwarded by a clinician, looking at the efficacy of aripiprazole in the treatment of children with irritability associated with autistic disorder (Marcus RN et al. J Am Acad Child Adolesc Psychiatry 2009; 48(11): 1110-9 and Owen R et al. Paediatrics 2009; 124(6): 1533-40). The Subcommittee noted that this is not a

registered indication in New Zealand but it has been registered for that use in the US since 2009. The Subcommittee noted that risperidone is registered for use in this indication but not all patients have a positive response to risperidone and some patients cannot tolerate the increase in weight gain (sometimes resulting in BMIs >30). The Subcommittee noted that low dose quetiapine is also used in some patients but it is not a registered indication in New Zealand.

3.6 The Subcommittee considered that the strength and quality of the evidence presented for aripiprazole for this indication was reasonable but the trials were of a short duration. The Subcommittee noted that there was no evidence presented for other treatment options. The Subcommittee noted that aripiprazole resulted in a 4 to 5 point greater improvement in the Aberrant Behaviour Checklist Irritability Subscale when compared to placebo and this is an acceptable response in this clinical setting. The Subcommittee considered that clinical experience suggests it is difficult to discontinue treatment after it is initiated but dose reduction is often attempted after 6 months. The Subcommittee considered that aripiprazole would sometimes be used in conjunction with SSRIs and stimulants for this indication. The Subcommittee considered that this is an area of unmet clinical need. The Subcommittee considered that about 1000-2000 children with autism are on an antipsychotic and a significant proportion of them would use aripiprazole if it is funded for this indication. The Subcommittee also considered that specialists should be involved when aripiprazole is initiated for this indication.

3.7 The Subcommittee noted that aripiprazole was included in the 2011/12 Tender for Hospital Sole Supply Status and as a result, there is a possibility that the drug cost would reduce. The Subcommittee **recommended** that if the Special Authority for aripiprazole is not removed as a result of price reductions from the tender, a funding application should be sought from the New Zealand branch of the Child and Adolescent Faculty of the Royal Australian and New Zealand College of Psychiatry (RANZCP) for aripiprazole in this indication.

3.8 The Subcommittee reviewed correspondence from a clinician forwarded on by Medsafe to the effect that there is an increased risk of breast cancer associated with raised prolactin levels and many antipsychotics cause hyperprolactinaemia and therefore should be avoided in patients with a history of breast cancer. The Subcommittee noted that the clinician believed that aripiprazole is theoretically of less a concern in this respect and therefore should be able to be used first line in patients with a history of breast cancer. The Subcommittee considered that there is currently insufficient evidence to support changing clinical practice in these patients and they should be monitored closely instead. The Subcommittee considered that that the Special Authority applying to aripiprazole should not be amended to waive the requirement for a prior trial of risperidone or quetiapine in patients with a history of breast cancer.

3.9 The Subcommittee considered that there was no clinical or safety reason to retain the monthly dispensing rule for buspirone and **recommended** that it be subject to a stat dispensing rule for funding purposes with high priority.

3.10 The Subcommittee noted that it had previously requested a review of melatonin to treat sleep/wake cycle problems or sleep onset difficulties in patients with dementia or neurodevelopmental problems (e.g autism). The Subcommittee reviewed clinical evidence forwarded by a clinician and the supplier for melatonin in patients with neurodevelopmental problems. The Subcommittee noted that Circadin (melatonin

modified-release 2mg) is now registered in New Zealand for use in primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over. The Subcommittee noted that Circadin is not registered in New Zealand or in other parts of the world for use in patients including children with secondary insomnia but trials are ongoing and the supplier intends to apply for indication-widening afterwards. The Subcommittee noted that in some European countries including France, the secondary insomnia indication is supported by the health authorities although it is off-label.

3.11 The Subcommittee noted that the supplier intends to submit a funding application to PTAC for Circadin in primary insomnia and will be willing to provide additional information on its use in secondary insomnia although it is not yet registered for that indication due to the interest from this Subcommittee.

3.12 The Subcommittee reviewed the clinical evidence for melatonin in patients with insomnia associated with neurodevelopmental problems forwarded by a clinician and considered that the evidence provided, although mainly small studies, does support its efficacy. The Subcommittee noted that alternative treatments for this patient group are promethazine, clonidine or over-the-counter melatonin preparations. The Subcommittee noted that benzodiazepines are not commonly used in children. The Subcommittee noted that no evidence was presented in regards to its use in patients with dementia. The Subcommittee noted that in the studies, melatonin was well tolerated but the long term risks are not well understood, including its possible effects on the onset of puberty.

3.13 The Subcommittee considered that funding melatonin for primary and/or secondary insomnia would be associated with a significant fiscal risk from widespread use. The Subcommittee **recommended** that a funding application be sought from the New Zealand branch of the Child and Adolescent Faculty of the Royal Australian and New Zealand College of Psychiatry (RANZCP) for the use of melatonin to treat sleep/wake cycle problems or sleep onset difficulties in patients with neurodevelopmental problems. The Subcommittee considered that this information, together with the information provided by the supplier can be reviewed by PTAC when it reviews Circadin for use in primary insomnia.

3.14 The Subcommittee considered the issue of widening access to atomoxetine for children with ADHD where the presence of tic disorders and when concerns regarding the increased risk of psychosis preclude the use of stimulants. The Subcommittee reviewed the clinical evidence forwarded by a clinician on the topic. The Subcommittee considered that clinical trials provide little evidence that stimulants worsen tic disorders. The Subcommittee noted that these patients are currently trialled on a low dose of methylphenidate and are switched to atomoxetine if their tic disorder worsens and this is appropriate. The Subcommittee **recommended** that access to atomoxetine be widened to include patients with ADHD who are at significant risk of developing psychosis if treated with methylphenidate or dexamphetamine with high priority. The Subcommittee noted that this patient group would be very small with less than 100 patients per year.

3.15 The Subcommittee noted that PHARMAC staff intend to consult shortly on declining Special Authority waivers for varenicline where the patient has failed to collect the full course of treatment within the stipulated Special Authority approval period of 5 months. The Subcommittee considered that this would be appropriate because the treatment should be taken as a 12-week continuous course.

4 Hyoscine (scopolamine) patches for clozapine-induced hypersalivation (CIH)

4.1 The Subcommittee reviewed an application from PHARMAC staff regarding hyoscine patches for the treatment of clozapine-induced hypersalivation (CIH). The Subcommittee noted that PHARMAC had received queries from clinicians about the possibility of widening funded access to hyoscine patches for this patient group. The Subcommittee noted that patients with CIH would not meet the current Special Authority criteria for hyoscine patches because the criteria requires patients to try other oral anti-nausea agents first but there is no evidence for these agents being effective for CIH.

4.2 The Subcommittee noted that there is very little clinical evidence for the use of hyoscine patches in this patient group with only two case reports. The Subcommittee however considered that it is unlikely that many clinical trials would be done for this treatment in this small patient group. The Subcommittee noted the results of a Cochrane review on the pharmacological interventions in this patient group (Syed et al. Cochrane Database of Systematic reviews 2008; Issue 3: Art No. : CD005579) which showed that there is very little evidence that any treatment was efficacious for CIH.

4.3 The Subcommittee noted that current treatment options for CIH include benztropine, atropine drops or terazosin. The Subcommittee noted that benztropine can cause constipation. The Subcommittee considered that hyoscine tablets were too short-acting and was not a good treatment option for CIH which is a significant problem when patients are asleep.

4.4 The Subcommittee noted that there are currently approximately 4000 patients on clozapine in New Zealand and 30% of them would have issues with CIH. The Subcommittee considered that 20% of those patients with CIH would not be responsive to first-line treatments like benztropine, atropine and/or terazosin. The Subcommittee noted that CIH is a significant issue which can lead to patients discontinuing treatment and this is not a good outcome because other antipsychotics have normally been proven ineffective in this patient group. The Subcommittee considered that hypersalivation associated with risperidone was more likely due to parkinsonism and hyoscine patches would not be an appropriate treatment in that situation.

4.5 The Subcommittee considered that although there is very little evidence for the use of hyoscine patches in CIH, it would be easy to ascertain clinical efficacy for this indication. The Subcommittee **recommended** that hyoscine patches is funded with high priority for patients with clozapine-induced hypersalivation. The Subcommittee recommended that the Special Authority restriction for hyoscine patches is amended as follows (additions in bold, deletions in strikethrough):

> Initial application - (**malignancy or chronic disease other than clozapine-induced hypersalivation)** from any relevant practitioner. Approvals valid for 1 year for applications meeting the following criteria:
> All of the following:
> 1 Control of intractable nausea, vomiting, or inability to swallow saliva in the treatment of malignancy or chronic disease; and
> 2 Patient cannot tolerate or does not adequately respond to oral anti-nausea agents; and
> 3 The applicant must specify the underlying malignancy or chronic disease.
>
> **Initial application - (clozapine-induced hypersalivation) from any relevant practitioner. Approvals valid for 3 months for patients who have clozapine-**

induced hypersalivation and trials with two other alternative treatment agents have proven ineffective.

Renewal from any relevant practitioner. Approvals valid for 1 year where the treatment remains appropriate and the patient is benefiting from treatment.

5 Omega-3 Fatty Acids for the Augmentation of Antipsychotics in Schizophrenia

5.1 The Subcommittee reviewed an application from PHARMAC staff in regards to the use of omega-3 fatty acids for the augmentation of antipsychotics in schizophrenia. The Subcommittee noted that some DHB hospitals are using these fatty acids (docosahexaenoic acid [DHA] 120mg with eicosapentaenoic acid [EPA] 180mg) for clozapine augmentation and the Hospital Pharmaceuticals Subcommittee of PTAC has requested advice from this Subcommittee on the matter.

5.2 The Subcommittee reviewed clinical evidence for this treatment in this indication and considered that the most relevant studies were the study by Peet M et al (Schizophrenia Research 2001; 29: 243-251) and a meta-analysis by Fusar-Poli et al (J Clin Psychopharmacol 2012; 32(2): 179-85). The Subcommittee noted that the meta-analysis revealed no beneficial effect of EPA augmentation in patients with schizophrenia.

5.3 The Subcommittee considered that the dosing regimen for omega-3 fatty acids required large doses of about 2g to 4g of EPA and/or DHA per day (amounting to about 10 capsules per day). The Subcommittee considered that patients are hesitant to take the treatment due to the dosing regimen required. The Subcommittee also considered that the capsules were quite large and unpleasant to take. The Subcommittee noted that weight gain was also an issue with long term use of these fatty acids.

The Subcommittee considered that there is currently insufficient evidence to support the use of omega-3 fatty acids for the augmentation of antipsychotics in schizophrenia. The Subcommittee **recommended** that omega-3 fatty acids are not listed in Section B or in a national Preferred Medicines List.