

Mental Health Subcommittee of PTAC
Meeting held 23 November 2016

(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 2016*.

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 9 & 10 February 2017, the record of which will be available in due course.

**Record of the Mental Health Subcommittee of the Pharmacology and Therapeutics
Advisory Committee (PTAC) meeting held at PHARMAC on 23 November 2016**

1 Correspondence / Matters Arising

Immunisation Subcommittee query regarding influenza vaccine

- 1.1 The Subcommittee noted that access to the influenza vaccine on the Hospital Medicines List (HML) was widened in August 2015 to include vaccination of patients who are compulsorily detained long-term in a forensic unit within a DHB hospital. The Subcommittee noted that in May 2016, the Immunisation Subcommittee of PTAC supported widening access to the influenza vaccine to include inpatients of long-term mental health care units with a high priority and recommended that PHARMAC seek advice from the Mental Health Subcommittee to define criteria for funding.
- 1.2 The Subcommittee noted its support for the Immunisation Subcommittee's interest in vaccinating patients in long-stay community units. The Subcommittee noted that the majority of mental health inpatients would be covered by existing funding criteria for the influenza vaccine. However, the Subcommittee considered that there may be some patient groups, for example patients with early onset dementia in long-stay geriatric care, who might not be covered. The Subcommittee was unsure as to how many patients would be in this situation but considered that the numbers would likely be low.
- 1.3 The Subcommittee **recommended** that the relevant criterion for the influenza vaccine on the HML be amended as follows (additions in bold):

Patients **in a long-stay inpatient mental health care unit or** who are compulsorily detained long-term in a forensic unit within a DHB hospital.

2 Paliperidone 3-Monthly Depot Injection

Application

- 2.1 The Subcommittee reviewed an application from Janssen-Cilag Pty Ltd for funding of paliperidone 3-monthly depot injection (Invega Trinza) for patients with schizophrenia who are stabilised on paliperidone 1-monthly depot injection (Invega Sustenna).

Recommendation

- 2.2 The Subcommittee **recommended** that paliperidone 3-monthly depot injection be listed on the Pharmaceutical Schedule only if cost-neutral to the Combined Pharmaceutical Budget.
- 2.3 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework for this recommendation.

Discussion

- 2.4 The Subcommittee noted that paliperidone 3-monthly depot injection is registered for use in adults with schizophrenia who have been adequately treated with paliperidone 1-monthly depot injection for at least four months.
- 2.5 The Subcommittee noted that the supplier's proposed funding restriction was for patients who have had "at least four once monthly depot injections of which at least the last two are the same dose". The Subcommittee noted that it would need to be clear that the four injections did not include the loading dose, as otherwise it would cover only three months of treatment.
- 2.6 The Subcommittee noted the high current expenditure on paliperidone 1-monthly depot (approximately \$8.85 million annually and growing rapidly).
- 2.7 The Subcommittee noted that despite the supplier's previous claims that dose titration was not needed with paliperidone 1-monthly injection, the supplier now acknowledges that this may be needed.
- 2.8 The Subcommittee reviewed two phase III trials provided by the supplier in support of the safety and efficacy of paliperidone 3-monthly depot injection.
- 2.9 The first (Berwaerts et al. JAMA Psychiatry 2015;72:830-839) was a randomised, double-blind, placebo-controlled, multicentre, relapse prevention study that evaluated the safety and efficacy of paliperidone 3-monthly depot injection vs. placebo in delaying time to relapse of schizophrenia symptoms in patients previously treated with paliperidone 1-monthly depot injection for at least 4 months. The Subcommittee noted that the findings of this study indicated that paliperidone 3-monthly depot injection has an antipsychotic effect compared with placebo, with a side effect profile consistent with what would be expected.
- 2.10 The second (Savitz et al. Int J Neuropsychopharmacol. 2016;1-14) was a randomised, double-blind, parallel-group, multicentre trial designed to test the non-inferiority of paliperidone 3-monthly depot injection to the 1-month formulation in patients with schizophrenia who were previously stabilised on paliperidone 1-monthly depot injection. The primary efficacy outcome was relapse rate at the end of a 48-week double-blind phase. The Subcommittee noted that this study reported the 3-monthly depot to be non-inferior to the 1-monthly formulation in terms of efficacy.
- 2.11 The Subcommittee considered that the studies were of moderate strength and low quality. The Subcommittee noted that neither trial was conducted in a 'real world' population. For example, the Subcommittee noted that the exclusion criteria in the Savitz study would have excluded a large number of patients that would typically be taking antipsychotic depot injections in the New Zealand clinical setting (including patients with suicidal risk, substance dependence, compulsory inpatients, obese people, people with significant co-morbid medical illness, and people on mood stabilisers or oral antipsychotics). The Subcommittee considered that the studies were conducted in a population that was a 'more well' population than would be seen in real clinical practice.

- 2.12 The Subcommittee noted that neither study measured quality of life for patients or carers, which is problematic because improved quality of life appeared to be a key rationale for funding the 3-monthly depot in the funding application. The Subcommittee considered that there were other problems with the trial designs, for example the dropouts in the lead-in period could result in a selection bias with 'problem' patients being excluded from the double-blind phase.
- 2.13 The Subcommittee noted that a key benefit of paliperidone 3-monthly depot injection claimed by the supplier was that the 3-monthly injection would allow more people to be transferred to primary care. The Subcommittee was unsure as to the extent that this would occur in clinical practice. The Subcommittee noted that currently less than 6% of antipsychotic depot prescribing occurs in primary care. Members considered that funding paliperidone 3-monthly depot injection would be unlikely to change this significantly.
- 2.14 The Subcommittee noted that transferring patients to primary care would shift costs to the patient in the 'user pays' primary care setting versus the funded secondary care mental health services. The Subcommittee considered that this could have a detrimental effect on patient care as patients were often ambivalent about treatment, and may often have low incomes due to their underlying disease, thus there may be problems with getting patients to attend primary care and pay for a treatment they may not want or be able to afford.
- 2.15 The Subcommittee noted that patients on antipsychotic depot injections benefit from secondary mental health services for mental state monitoring and relapse prevention, side effect monitoring/medication intolerance, assistance with coexisting disorders and substance abuse, rehabilitation support including skill retrieval/development, social assistance/housing, and other support. The Subcommittee noted that while there are some good models of primary health liaison where mental health nurses in primary care could ensure good follow-up, this was not consistent throughout the country and many primary care centres would not be adequately resourced to manage and work with these patients.
- 2.16 The Subcommittee noted that while it was possible that a three-monthly depot injection could result in fewer healthcare visits for patients, no good evidence was provided by the supplier to support this. The Subcommittee considered that the 3-monthly depot injections was unlikely to provide savings to the health system as suggested in the application, as healthcare workers such as mental health nurses travel to see patients for many reasons other than just administering depot injections, and these activities would be expected to continue on a regular basis. The Subcommittee noted that decreased contact with mental health carers was not necessarily beneficial, as it could lead to reduced psychosocial monitoring patient disengagement and their greater isolation.
- 2.17 The Subcommittee considered that the only potential savings to the health system would be if the 3-monthly depot resulted in fewer hospitalisations; however, there was no data to support this.
- 2.18 Overall, the Subcommittee considered that the supplier's funding application was of poor quality, with overstated benefits and inconsistent cost effectiveness claims and with neither of the key two phase III clinical trials providing any information

about the impacts of paliperidone 3-monthly depot injection on the patient population likely to be prescribed it in New Zealand.

- 2.19 The Subcommittee noted data provided in the supplier's submission that had been obtained from PHARMAC and appeared to indicate a high attrition rate for patients starting on antipsychotic depot injections. The Subcommittee was surprised by the data and requested that PHARMAC look into this further and present updated analysis on this, including determining what (if any) treatment patients took once they stopped taking the particular depot injection.
- 2.20 The Subcommittee considered that the main potential benefits of the 3-monthly depot injection over the 1-monthly formulation would be patient preference and flexibility around dose follow up (as administration could occur two weeks before or after its due date) – although the longer time between doses may make it harder to keep track of “difficult to find” patients, noting that it is not uncommon for patients on depot antipsychotics to move or avoid contact.
- 2.21 The Subcommittee considered that there was a small group of patients in both primary and secondary care who did not require monthly visits from a healthcare professional who would likely benefit from a 3-monthly depot injection.
- 2.22 The Subcommittee considered that disadvantages of the 3-monthly depot injection over the monthly formulation included the longer duration of time for the pharmaceutical to be eliminated from a patient's system if they experienced side-effects and the lack of long-term safety data for the 3-monthly preparation.
- 2.23 The Subcommittee considered that it was reasonable to assume that most patients receiving antipsychotic depot injections would prefer less frequent injections, and for this reason members considered that the uptake would be very high if the 3-monthly depot injection were funded – probably similar to what has occurred with the switch from risperidone to paliperidone 1-monthly injection. The Subcommittee considered that the availability of a funded 3-monthly depot would also likely result in more patients taking depot injections overall, potentially to the same extent that listing paliperidone 1-monthly depot injection has done.
- 2.24 The Subcommittee considered that there was no clinical reason not to fund paliperidone 3-monthly depot injection; however, there was insufficient justification for this to result in an increased cost per patient versus paliperidone 1-monthly injection or increased expenditure to the Combined Pharmaceutical Budget.

3 Memantine for Treatment-Resistant Schizophrenia

Application

- 3.1 The Subcommittee reviewed information from PHARMAC staff and Named Patient Pharmaceutical Assessment (NPPA) applicants in relation to the use of memantine as an adjunctive treatment in patients with treatment-resistant schizophrenia.

Recommendation

- 3.2 The Subcommittee **recommended** that the funding of memantine as an adjunctive therapy in patients with treatment-resistant schizophrenia be declined.

Discussion

- 3.3 The Subcommittee noted that following the receipt of 3 Named Patient Pharmaceutical Assessment (NPPA) applications in quick succession for memantine for augmentation of antipsychotic effect in patients with treatment-resistant schizophrenia, PHARMAC considered it would be more appropriate to consider funding of memantine for this patient group via the Pharmaceutical Schedule and sought the Mental Health Subcommittee's clinical advice.
- 3.4 The Subcommittee noted that patients with severely treatment-resistant schizophrenia were very disabled and usually institution bound, and as such had very high health need. The Subcommittee noted that a goal of augmentation with memantine would be to provide some cognitive enhancement for these patients to enable them to participate more fully in their treatment and gain some quality of life.
- 3.5 The Subcommittee considered that most patients with severely treatment-resistant schizophrenia would be taking clozapine, so it would be reasonable to assume the potential patient pool (ie. numbers of patients) for memantine as augmentation would be similar to or less than the clozapine patient pool.
- 3.6 The Subcommittee reviewed the following publications:
- de Lucena et al. J Clin Psychiatry 2009;70:1416-1423: a randomised, double blind, placebo-controlled study in 21 patients with refractory schizophrenia treated with memantine (n=10; 5 mg/day titrated to a maximum of 20 mg/day) or placebo (n=11) in addition to clozapine for 12 weeks.
 - Lieberman et al. Neuropsychopharmacology 2009;34:1322-9: an 8-week randomised double-blind, placebo-controlled trial in 138 patients with persistent residual psychopathology of schizophrenia treated with memantine (n=70, 20 mg/day) or placebo (n = 68), in addition to continuing treatment with atypical antipsychotics.
 - Lee et al. Psychiatry Investig 2012;9:166-73: a 12-week, randomised, placebo-controlled trial in 26 patients with chronic schizophrenia treated with memantine (n=15; 5 mg/day titrated to a maximum of 20 mg/day) or placebo (n=11) in addition to their antipsychotic medication.
 - Rezaei et al. J Clin Psychopharmacol 2013;33:336-342: an 8-week, double-blind randomised placebo-controlled trial in 40 patients with stable schizophrenia treated with memantine (n=20; 20 mg/day) or placebo (n=20) in addition to risperidone (6 mg/day).
 - Omranifard et al. Adv Biomed Res 2015;4:211: a 12-week, randomised, double-blind, placebo-controlled trial in 64 inpatients with schizophrenia treated with memantine (n=32; 5 mg/day titrated to a maximum of 20 mg/day) or placebo (n=32) in addition to their previously administered treatment.
 - Veerman et al. Psychol Med 2016;46:1909-21: a 26 week study of memantine augmentation in 52 patients with clozapine-refractory schizophrenia. Patients were randomly assigned to 12 weeks of double-blind adjunctive treatment with memantine (n = 26) or placebo (n = 26).

- 3.7 The Subcommittee noted that the above studies were all of relatively short duration. The Subcommittee considered that given the mechanism of action of memantine, it did not make biological sense to conduct short-term studies.
- 3.8 The Subcommittee noted that the primary outcomes of the studies were variable and noted that no study had settled on the primary benefit of memantine, whether through cognitive improvement or assistance with clozapine side effects. Members further noted that none of the studies were sufficiently powered to be pivotal to any advice, and only one study had reported power calculations for the number of patients or events required to determine statistically significant results.
- 3.9 Overall, the Subcommittee considered that the current evidence base (including the lack of any identified meta-analyses with no statistical heterogeneity) did not support the use of memantine as an adjunctive therapy for patients with treatment-resistant schizophrenia and, therefore, there was insufficient justification for funding it for this indication.
- 3.10 The Subcommittee noted that it was sympathetic to the desire for clinicians to want to try new treatment approaches for their patients and indicated that it would be willing to review its recommendation if higher-quality supportive evidence become available.

4 Midazolam Injection on PSO

- 4.1 The Subcommittee noted that following two requests received by PHARMAC to make midazolam injection 5 mg per ml, 3 ml available on a Practitioners Supply Order (PSO) for use in seizure control, PHARMAC was seeking advice from both the Neurological and Mental Health Subcommittees on the appropriateness of the requests.
- 4.2 The Subcommittee considered that there was a risk of addiction to midazolam and making it more available could increase this risk, although this would likely be low given the strict requirements around storage of controlled drugs.
- 4.3 The Subcommittee noted that it would be difficult to restrict its use to seizure control on PSO as, once acquired, it could be used for any other relevant indication. Members noted that there were no particular mental health indications for its use.
- 4.4 The Subcommittee considered that there could be a place for PSO use in a rural setting but that urban general practices may be less likely to encounter patients having a seizure.
- 4.5 Members noted that it was possible to use oral lorazepam for seizure control. However, the Subcommittee considered that the key advantages of using midazolam for seizure control are its rapid onset of action and that it can be given nasally or buccally.
- 4.6 The Subcommittee considered that it would be important to have the 1 mg per ml, 5 ml presentation available as there would be less risk of overdose in a child.

- 4.7 The Subcommittee considered, on balance, it would be a useful option to make midazolam injection available on PSO for seizure control.

5 Lamotrigine

- 5.1 The Subcommittee noted that PHARMAC was in the planning stages of running a commercial process that could result in only one brand of lamotrigine being funded. The Subcommittee considered that it would not be clinically problematic from a mental health standpoint to switch patients from one brand to another if necessary (ie. no more or less problematic than any other mood stabiliser brand change), although it would require additional work by pharmacists to reassure patients who were switched. The Subcommittee noted that brand switching in the lamotrigine market already occurred, as there are multiple funded brands.
- 5.2 The Subcommittee considered that a lamotrigine brand change in patients taking it for mental health indications would be unlikely to require additional clinic visits.
- 5.3 The Subcommittee considered that a 3-6 month transition for a funded brand change/sole supply, as suggested by the Neurological Subcommittee, seemed like a sensible implementation timeframe from a mental health perspective.
- 5.4 The Subcommittee considered that PHARMAC's usual brand switch activities would be sufficient to support a lamotrigine brand change from a mental health perspective. The Subcommittee noted that because lamotrigine is in its own class, pharmacologically speaking, amongst mood stabilisers, some patients may be particularly dependent on it psychologically and may need extra support.