Mental Health Subcommittee of PTAC meeting held 21 June 2010

(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 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.

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA) in order to:

(i) protect information where the making available of the information would be likely to unreasonably prejudice the commercial position of the person who supplied or who is the subject of the information (section 9(2)(b)(ii));
(ii) protect information which is subject to an obligation of confidence or which any person has been or could be compelled to provide under the authority of any enactment, where the making available of the information would be likely to prejudice the supply of similar information, or information from the same source, and it is in the public interest that such information should continue to be supplied (section 9(2)(ba)(i)); and/or
(iii) enable PHARMAC to carry on, without prejudice or disadvantage, negotiations (including commercial and industrial negotiations (section 9(2)(j)).

These Subcommittee minutes were reviewed by PTAC at its meeting on 5 & 6 August 2010, the record of which is available on the PHARMAC website.

Contents

1 Rivastigmine capsules and rivastigmine patches

1.1 The Subcommittee reviewed an application from Novartis New Zealand Limited for funding of rivastigmine transdermal patches (Exelon) and from [withheld under s9(2)(b)(ii), s9(2)(ba)((i) and/or s9(2)(j) of the OIA] for funding of rivastigmine capsules [withheld under s9(2)(b)(ii), s9(2)(ba)((i) and/or s9(2)(j) of the OIA]. The Subcommittee noted that subsequent to the announcement of the funding decision for donepezil (which is due to be funded without restrictions once the Donepezil-Rex brand is registered), the suppliers were proposing that their products be funded for the second-line treatment of Alzheimer's disease (ie, in patients who could not tolerate donepezil).

1.2 The Subcommittee considered that there was good evidence to suggest that acetylcholinesterase inhibitors, including rivastigmine, delay Alzheimer's disease progression by approximately 6–12 months. Members noted that no data were provided on the second-line use of acetylcholinesterase inhibitors.

1.3 The Subcommittee considered that the evidence suggested that acetylcholinesterase inhibitors would also provide benefit in patients with other types of dementia such as Lewy body dementia; however, members noted that rivastigmine was only indicated for use in mild to moderately severe Alzheimer's disease.

1.4 The Subcommittee considered that the target dose for rivastigmine capsules was 9–12 mg daily, although members noted that, in their experience, patients had difficulty achieving the higher end of this range because of tolerability problems. Members also noted that it generally takes up to 3 months to reach the target dose of rivastigmine capsules. The Subcommittee considered that the target dose for rivastigmine patches was 9.5 mg/24 h (ie, one 10 cm^2 patch per day). Members considered that rivastigmine patches were better tolerated than rivastigmine capsules.

1.5 The Subcommittee considered that donepezil tablets 5 mg and 10 mg per day provided similar efficacy to rivastigmine capsules 3–6 mg and 9–12 mg, respectively, per day. The Subcommittee considered that rivastigmine patches 5 cm^2 and 10 cm^2 per day provided similar efficacy to rivastigmine capsules 3–6 mg and 9–12 mg, respectively, per day. Members considered that a 5 cm^2 rivastigmine patch was subtherapeutic, but was useful for titration.

1.6 The Subcommittee considered that approximately 15% of patients cannot tolerate the gastrointestinal side effects of donepezil, particularly at the higher (10 mg per day) dose, which generally leads to treatment discontinuation. Members considered that this would be the main reason that most people discontinued donepezil treatment, noting that most patients do not have any particular difficulty swallowing tablets.

1.7 The Subcommittee considered that it was likely that most patients who cannot tolerate donepezil would also not be able to tolerate the gastrointestinal side effects of rivastigmine capsules. Therefore, the Subcommittee considered that it would not make clinical sense to restrict funding of rivastigmine capsules to second-line treatment in patients who cannot tolerate donepezil.

1.8 When considering rivastigmine capsules as a first-line treatment (ie as an alternative to donepezil), the Subcommittee considered that there were some advantages of donepezil tablets over rivastigmine capsules, in that donepezil can be taken once daily whereas rivastigmine capsules are given twice daily, donepezil tablets are generally better tolerated than rivastigmine capsules and the time to get to target dose is generally shorter with donepezil.

1.9 The Subcommittee noted that the gastrointestinal side effects of rivastigmine are significantly reduced with transdermal patch application; therefore, the Subcommittee considered that rivastigmine patches would be beneficial for patients who could not tolerate donepezil tablets. The Subcommittee noted that rivastigmine patches are associated with application site reactions, which led to treatment discontinuation in a small proportion (1%–2%) of patients in clinical trials.

1.10 The Subcommittee noted that there was an increasing number of Maori and Pacific Islanders presenting with dementia, and that access to treatments for these patient groups was poor compared to the general population.

1.11 The Subcommittee considered that there was no clinical reason to restrict access to funded rivastigmine patches or rivastigmine capsules; however, the Subcommittee considered that it would be reasonable, on a cost basis, to restrict access to rivastigmine patches to patients who cannot tolerate donepezil tablets.

1.12 The Subcommittee noted that it would be difficult for most patients with dementia to self-administer rivastigmine patches, so most patients taking the patches would have good compliance because their caregiver would ensure that the patch had been applied.

1.13 The Subcommittee considered that rivastigmine patches, if restricted to second-line treatment, would not affect the market dynamics of alternative treatments. Members considered that there may be a patient preference advantage associated with rivastigmine patches but that this would unlikely to affect uptake to a significant degree.

1.14 The Subcommittee **recommended** that rivastigmine capsules be listed on the Pharmaceutical Schedule only if they were no more expensive than donepezil.

1.15 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

1.16 The Subcommittee further **recommended** that rivastigmine patches be listed on the Pharmaceutical Schedule subject to Special Authority criteria restricting its use to patients who cannot tolerate donepezil tablets. The Subcommittee considered that, within the context of the mental health therapeutic area, this recommendation should be considered a medium priority.

1.17 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.

2 Paliperidone depot injection

2.1 The Subcommittee reviewed an application from Janssen-Cilag for funding of paliperidone depot injection (Invega Sustenna) for the treatment of schizophrenia, subject to the same Special Authority criteria as risperidone depot injection (Risperdal Consta).

2.2 The Subcommittee noted that paliperidone is the major active metabolite of risperidone (9-hydroxyrisperidone) and that it undergoes minimal hepatic metabolism.

2.3 The Subcommittee noted that the supplier had provided one unpublished randomised double blind study (PSY-3006) comparing paliperidone depot injection with risperidone depot injection. The Subcommittee disagreed with the supplier's assertion that study population in this trial was representative of the New Zealand population, noting that it did not appear to have any Maori or Pacific Island participants and it had excluded patients with co-morbidities that are common in clinical practice, such as patients with active substance dependence, unstable medical conditions or a significant risk of suicidal or violent behaviour. The Subcommittee considered that the results of PSY-3006 suggest that paliperidone depot injection is non-inferior to risperidone depot injection in terms of efficacy and that the two treatments have similar adverse event profiles.

2.4 The Subcommittee considered that paliperidone depot injection would also provide similar therapeutic effect to olanzapine depot injection as well as the funded older antipsychotic depot injections, some of which could be administered monthly.

2.5 The dosing schedule for paliperidone depot injection is 150 mg on day 1 followed by 100 mg on day 8. The maintenance dose range is 25–150 mg monthly, which the Subcommittee considered compares to risperidone depot injection 25–50 mg fortnightly. The Subcommittee considered that this dosing schedule could make paliperidone depot injection easier to use than risperidone depot injection in the initial stages.

2.6 The Subcommittee noted that a key advantage claimed for paliperidone depot injection is that it does not require supplementation with oral antipsychotics in the initial dosing stages prior to achieving steady state, based on pharmacokinetic data suggesting that the therapeutic dose is achieved quickly. However, the Subcommittee noted that in PSY-3006 five patients (all in the paliperidone group) discontinued treatment due to schizophrenia, agitation, paranoia and psychosis which, along with the higher percentage of patients requiring benzodiazepine supplementation (34% in the paliperidone group versus 28% in the risperidone group) in the trial suggests that in clinical practice some cover with oral antipsychotics would probably be needed. The Subcommittee considered that paliperidone depot injection would also be used in

2.7 The Subcommittee noted that paliperidone depot injection does not require refrigeration and comes in a prefilled syringe.

2.8 The Subcommittee considered that there were no particular problems with access to funded alternative treatments. The Subcommittee considered that it would be useful to have access to another funded atypical antipsychotic depot injection; however, members considered that paliperidone depot injection would not sufficiently address this given its similarity to risperidone depot injection.

2.9 The Subcommittee considered that there was no compelling evidence presented to suggest that paliperidone depot injection would improve compliance compared with risperidone depot injection. Members considered that patients who were disengaged and did not want fortnightly injections were unlikely to have improved engagement and adherence if given the option of a monthly injection.

2.10 The Subcommittee considered that there were potentially significant disadvantages associated with monthly injections if the effect of that was that patients are seen less often. The Subcommittee noted that the patient group taking depot antipsychotics were those with severe psychotic illness, generally requiring frequent contact to encourage patient engagement, monitor their mental state and to assess how the medication is working and how well it is tolerated. Members noted that more frequent contact also allows working with families, developing rehabilitation goals and looking at psychoeducation and strategies for relapse prevention. Members noted that people with severe psychotic illnesses can change address frequently and less regular contact can lead to a higher rate of patients being lost to the service. The Subcommittee noted that less planned contact could lead to a delay in noticing signs of relapse.

2.11 The Subcommittee noted that the principles of Assertive Community Treatment have frequent service engagement and follow-up as one of the key component in determining improved outcomes for people with serious mental illness/schizophrenia. Members noted that service development (eg Assertive Community Treatment and culturally responsive services) for Maori and Pacific Islanders with mental illness, and for patients with mental illness in prisons, rely on increased service contact and therapeutic engagement.

2.12 Therefore, the Subcommittee considered that even in cases where a monthly depot injection antipsychotic injection might be useful (eg in the ~10%–20% of relatively stable patients where compliance remains an issue), it would still be preferable to maintain frequent nurse visits and this would probably continue to occur in any case.

2.13 The Subcommittee considered that from the evidence provided it was not clear if paliperidone depot injection would provide any advantages for Maori or Pacific Island people with schizophrenia; however, members considered that there could be some disadvantages from less intense service engagement.

2.14 The Subcommittee considered that there were no clinical reasons to place any restrictions on the use of paliperidone depot injection; however, given its cost it would be reasonable to place it under restrictions similar to risperidone depot injection. The

Subcommittee considered that if paliperidone depot injection was funded it would be highly promoted and would grow the antipsychotic depot market, largely at the expense of risperidone depot injection.

2.15 The Subcommittee noted that a cost-utility analysis (CUA) was included in the application, and that PHARMAC staff had amended several inputs and assumptions in the analysis. It was noted that the PHARMAC-amended analysis reported a cost per quality adjusted life year (QALY) for paliperidone depot injection of approximately $390,000. The Subcommittee considered that the adjustment of the monthly dose from 91 mg in the supplier's analysis to 138 mg was reasonable and that an assumption of a 20% reduction in nurse visits was reasonable. The Subcommittee also considered that the adjustment in QALY gain from 0.047 to 0.003 was reasonable.

2.16 The Subcommittee noted that the supplier's estimate of quality of life used in its CUA assumed patients are required to travel to get their medication using public transport; however, the Subcommittee considered that the majority of patients in New Zealand do not travel to receive their medication as community nurses visit their homes to deliver it.

2.17 The Subcommittee **recommended** that paliperidone depot injection be listed on the Pharmaceutical Schedule subject to Special Authority criteria similar to risperidone depot injection. The Subcommittee considered that, within the context of the mental health therapeutic area, this recommendation should be considered a low priority.

2.18 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples (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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

3 Quetiapine modified-release tablets

3.1 The Subcommittee reviewed an application from AstraZeneca for funding of quetiapine modified-release tablets (Seroquel XR), a once-daily preparation of quetiapine.

3.2 The Subcommittee noted that PHARMAC currently funds quetiapine immediate-release tablets (Seroquel and Quetapel). The Subcommittee noted that quetiapine is currently approved by Medsafe for use in acute and chronic psychoses, including schizophrenia, and treatment of bipolar disorder (manic and depressive episodes and maintenance treatment). However, the Subcommittee considered that quetiapine is also currently widely used off-label at low doses as a sedative, particularly in the elderly, and in anxiety disorders. The Subcommittee noted that this view is supported by the average daily dose data, which show that the majority of patients are receiving less than 100 mg per day.

3.3 The Subcommittee noted that the supplier had provided reasonably good evidence that quetiapine modified-release tablets provide similar efficacy to quetiapine immediate-release tablets.

3.4 The Subcommittee noted that the major difference between the two preparations was their pharmacokinetic profiles, with the modified-release preparation having smoother pharmacokinetics and the immediate-release preparation having greater peaks and troughs. However, the Subcommittee noted that there was no evidence of a difference in side effects between the two preparations in the clinical trials and members considered that the supplier had not provided evidence to support a claim of improved tolerability.

3.5 The Subcommittee considered that the supplier had not provided clear evidence to support its claim that up-titration would be faster with quetiapine modified-release compared with the immediate-release preparation.

3.6 The Subcommittee noted that, according to the prescribing data provided by PHARMAC staff, the majority of patients in all dose groups (approximately 75% of patients overall) are currently prescribed quetiapine immediate-release to be taken once-daily (as opposed to twice-daily or more frequently). The Subcommittee considered that the remainder of patients probably did not have a big issue with compliance. The Subcommittee considered that quetiapine modified-release tablets were unlikely to provide a significant compliance advantage over the immediate-release preparation in the population as a whole.

3.7 The Subcommittee considered that there were some theoretical advantages of the modified-release preparation in patients who have problematic peak/trough effects from the immediate-release preparation at higher doses (eg dizziness and somnolence) although there was no evidence to support this.

3.8 The Subcommittee considered that if quetiapine modified-release tablets were funded they would largely replace the use of quetiapine immediate-release tablets, with the possible exception of patients on very low doses, because there would be a perception that they would be better tolerated.

3.9 The Subcommittee noted that this would be associated with a significant fiscal risk, given the current status of the quetiapine tablet market in terms of competition and patent expiry.

3.10 The Subcommittee considered that there was no clinical reason not to fund quetiapine modified-release tablets and, therefore, **recommended** that quetiapine modified-release tablets be listed on the Pharmaceutical Schedule. The Subcommittee considered that, within the context of the mental health therapeutic area, this recommendation should be considered a low priority.

3.11 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples (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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*