Mental Health Subcommittee of PTAC meeting held 31 July 2009

(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 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 following withholding grounds of the Official Information Act 1982 (OIA) to enable a Minister of the Crown or any department or organisation holding information to carry on, without prejudice or disadvantage, negotiations (including commercial and industrial negotiations (section 9(2)(j)).

Contents

1 Mirtazapine

1.1 The Subcommittee noted that the listing of mirtazapine under Special Authority restrictions (with the criteria as consulted on) has been approved, with listing to occur as soon as the necessary Medsafe consents have been granted.

1.2 The Subcommittee noted that during consultation on a proposal to fund mirtazapine PHARMAC had received requests from several consultation responders to change the proposed access criteria, to include patients with moderate depression and patients intolerant to other antidepressants and to allow the use of mirtazapine as a first-line option in psychogeriatric patients and those in whom the presence of significant co-morbidities such as cancer and HIV infection would preclude the use of other antidepressants.

1.3 The Subcommittee considered that, given the significant price differential between mirtazapine and most other funded antidepressants, restricting its use to patients with severe depression was appropriate at this time.

1.4 The Subcommittee considered that the request to include patients intolerant to other antidepressants was reasonable and, accordingly, **recommended** that the relevant criteria be amended to the following (additions in bold):

Initial application from any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:
Both:

1 The patient has a severe major depressive episode; and
2 Either:
  2.1 The patient must have had a trial of two different antidepressants and **was unable to tolerate the treatments or** failed to respond to an adequate dose over an adequate period of time (usually at least four weeks); or
  2.2 Both:
    2.2.1 The patient is currently a hospital in-patient as a result of an acute depressive episode; and
    2.2.2 The patient must have had a trial of one other antidepressant **and either could not tolerate it or** failed to respond to an adequate dose over an adequate period of time.

Renewal from any relevant practitioner. Approvals valid for 2 years where the patient has a high risk of relapse (prescriber determined).

1.5 The Subcommittee considered that if the Special Authority was amended as proposed it would have very little effect (if any) on the estimated usage.

1.6 The Subcommittee considered that there were other, less expensive, first-line antidepressant treatment options, for example selective serotonin reuptake inhibitors,

moclobemide, and tricyclic agents, that it would be reasonable to consider for psychogeriatric patients or those with significant co-morbidities and, therefore, there was no compelling reason to change the criteria for mirtazapine to allow first-line use in these patient groups. The Subcommittee noted that it would be willing to reconsider the issue if evidence was provided in support of the use of mirtazapine instead of the other treatment options as a first-line agent in these patient groups.

1.7 The Subcommittee noted that PHARMAC staff had been considering the possibility of further restricting venlafaxine by amending the Special Authority criteria to require a trial of mirtazapine prior to accessing funded venlafaxine. The Subcommittee considered that this would not be necessary as it was likely to happen anyway once mirtazapine was funded. The Subcommittee noted that mirtazapine was not without side effects, in particular it is quite sedating and can be associated with weight gain, and it is also associated with rare, but potentially fatal, bone marrow suppression.

2 Mianserin

2.1 The Subcommittee noted that the Royal Australian New Zealand College of Psychiatrists had requested a review of the restrictions applying to mianserin because the College considers that mianserin would be useful in other clinical situations, in particular because of it being sedating without being anticholinergic or cardiotoxic.

2.2 The Subcommittee noted that there are few funded options for patients who do not meet the current mianserin restrictions (i.e. patients who do not have bladder neck obstruction or cardiovascular disease) and who require treatment with a non-serotonergic antidepressant, particularly if they cannot tolerate nortriptyline.

2.3 For this reason, the Subcommittee **recommended** that the Special Authority criteria for mianserin be amended to the following:

Initial application from any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:
Either:
1 Both:
  1.1 The patient has depression; and
  1.2 Either:
    1.2.1 The patient has co-existent bladder neck obstruction; or
    1.2.2 The patient has cardiovascular disease; or
2 Both:
  2.1 The patient has a severe major depressive episode; and
  2.2 Either:
    2.2.1 The patient has had a trial of two different antidepressants and was unable to tolerate the treatments or did not respond to an adequate dose over an adequate period of time (usually at least four weeks); or
    2.2.2 Both:

2.2.2.1 The patient is currently a hospital in-patient as a result of an acute depressive episode; and

2.2.2.2 The patient has had a trial of one other antidepressant and was either unable to tolerate it or failed to respond to an adequate dose over an adequate period of time.

Renewal from any relevant practitioner. Approvals valid for 2 years where the patient has a high risk of relapse (prescriber determined).

2.4 The Subcommittee considered that if the Special Authority was amended as proposed the use of mianserin would not increase greatly, and any increase would likely be mainly at the expense of venlafaxine use.

2.5 The Subcommittee considered that, within the context of the mental health therapeutic area, this recommendation should be considered a high priority, assuming that it would be cost neutral or cost saving to the Pharmaceutical Budget.

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; (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 Duloxetine hydrochloride

3.1 The Subcommittee reviewed an application from Eli Lilly for funding of duloxetine hydrochloride (Cymbalta) for the treatment of major depressive disorder that is not responsive to other antidepressants. The Subcommittee noted that PTAC had reviewed the application in July 2008 and had recommended that the application for funding of duloxetine be deferred pending a review by the Mental Health Subcommittee of PTAC and receipt of further information from the supplier regarding the efficacy of duloxetine in patients who had received suboptimal benefit from previous treatments. The Subcommittee noted that the supplier has subsequently advised that no such data are available.

3.2 The Subcommittee noted that the supplier had not provided any placebo-controlled studies in its application; however, the majority of the studies identified in a literature search demonstrated superiority of duloxetine over placebo and members noted that this would have been a requirement for registration by Medsafe.

3.3 The Subcommittee noted that the supplier had provided one publication in support of its application (Perahia et al. J Psychiatr Res 2008;42(1):22-24). This was a report of

pooled results from two randomised, double-blind, parallel, outpatient studies comparing duloxetine (n=330) with venlafaxine (n=337) in patients with major depressive disorder; data from the studies were designed to be pooled *a priori* in the protocol for the primary analysis. Patients were treated with duloxetine 60 mg or venlafaxine 75 mg and 150 mg for 12 weeks. The primary outcome measure was non-inferiority of duloxetine compared to venlafaxine, based on mean change in Hamilton Depression Rating Scale (HAMD) score.

3.4 The Subcommittee considered that the study was of good quality, although non-inferiority of duloxetine to venlafaxine was not convincingly demonstrated. However, the Subcommittee considered that from the evidence provided it would be reasonable to assume that duloxetine would probably provide similar efficacy to venlafaxine at equivalent doses. The Subcommittee also considered that duloxetine would likely provide similar efficacy to other funded antidepressants.

3.5 The Subcommittee noted that duloxetine is associated with a risk of elevated liver transaminases; however, members noted that the incidence of severe hepatotoxicity appeared to be low. Other side effects included nausea, sexual dysfunction and, rarely, hyponatraemia. The Subcommittee noted that nausea tended to occur early in treatment and could be reduced by reducing the starting dose or by taking duloxetine with food.

3.6 The Subcommittee noted that duloxetine, unlike venlafaxine, appears to act as a selective serotonin and noradrenaline reuptake (SNRI) at all doses whereas venlafaxine acts as a selective serotonin reuptake inhibitor (SSRI) at doses of less than 150 mg per day and as an SNRI at doses greater than 150 mg per day. However, the Subcommittee noted that, likely as a result of the restrictions on venlafaxine, the average daily dose of venlafaxine in New Zealand was relatively high, at approximately 170 mg per day, so both duloxetine and venlafaxine would be acting as SNRIs if both were funded under restrictions similar to the venlafaxine restrictions.

3.7 The Subcommittee considered it was likely that doses greater than 60 mg/day of duloxetine would be used in clinical practice, particularly in patients who had not responded adequately to treatment with other agents. The Subcommittee noted that in the clinical study approximately 30% of patients had taken 90 mg per day and 17% of patients had taken 120 mg per day. The Subcommittee considered that under the proposed restrictions the average daily dose could be in the region of 80 mg per day. The Subcommittee noted that the incidence and severity of adverse events could increase at higher doses.

3.8 The Subcommittee considered that under the proposed restrictions duloxetine would mainly be used as an alternative to venlafaxine and mirtazapine, but that there would also likely be a small (5%) movement from the SSRI market.

3.9 The Subcommittee considered that there were currently no problems with access to antidepressant treatments, and that duloxetine would not provide any particular benefits or risks over currently funded treatments.

3.10 The Subcommittee considered that there was the potential for off-label use of duloxetine, for example in anxiety or pain management; however, the Subcommittee considered that such usage would be negligible under the proposed criteria.

3.11 The Subcommittee considered that there was an unmet clinical need for a second/third-line antidepressant for patients who were hypertensive (and, therefore could not take venlafaxine) or susceptible to weight gain (in whom mirtazapine would not be suitable); however, members were unsure as to whether duloxetine would adequately meet this need.

3.12 The Subcommittee noted that no evidence had been provided in support of duloxetine in patients who had failed to respond to other treatments; however, the Subcommittee considered that it would be reasonable to restrict duloxetine to this patient group given the high price of duloxetine compared with the funded SSRIs and tricyclic antidepressants.

3.13 The Subcommittee **recommended** that duloxetine be listed in the Pharmaceutical Schedule, subject to Special Authority restrictions similar to those applying to mirtazapine, only if this would be cost-neutral or a saving to the Pharmaceutical Budget.

3.14 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.*

4 Sertraline hydrochloride

4.1 The Subcommittee noted that it had reviewed the funding of sertraline hydrochloride in May 2008 and had recommended funding sertraline only if it was cost-neutral to the Pharmaceutical Budget. It was noted that, at the time, the Subcommittee considered that there were no significant benefits or risks of sertraline compared with currently funded selective serotonin reuptake inhibitors (SSRIs) antidepressants and that there was no unmet clinical need that could be met by funding sertraline.

4.2 The Subcommittee reviewed a recent meta-analysis conducted to assess the effects of 12 new-generation antidepressants on depression (Cipriani et al, Lancet 2009;373:746-758). Members noted that the study employed relatively new methodology, a multiple-treatments meta-analysis, which accounts for both direct and indirect comparisons.

4.3 The Subcommittee noted that the results of the multiple-treatments meta-analysis suggest that mirtazapine, escitalopram, venlafaxine and sertraline are significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine and reboxetine, with escitalopram and sertraline showing the best profile of acceptability. The study's authors concluded that sertraline might be the best choice of first-line treatment for moderate-to-severe major depression because "it has the most favourable balance between benefits, acceptability, and acquisition cost."

4.4 The Subcommittee considered that the study was of good strength and quality; however, members noted that the study had received some criticism, particularly around the completeness of data collection (e.g. suggestions that some data may have been withheld by pharmaceutical companies).

4.5 The Subcommittee also reviewed a publication from the Cochrane collaboration (Cipriani et al, Cochrane Database of Systematic Reviews 2009; Issue 2. Art.No.: CD006117) which assessed the evidence for the efficacy, acceptability and tolerability of sertraline in comparison with tricyclics (TCAs), heterocyclics, other SSRIs and newer agents in the acute-phase treatment of major depression. The authors concluded that the review and meta-analysis highlighted a trend in favour of sertraline over other antidepressive agents both in terms of efficacy and acceptability. However, again, the Subcommittee considered that the clinical relevance of this finding was unclear.

4.6 The Subcommittee reiterated its previous view that there was no clinical reason to place a restriction on the use of sertraline; however, given that sertraline is currently significantly more expensive than the funded SSRIs, listing it under similar restrictions to mirtazapine would be a reasonable approach.

4.7 The Subcommittee considered that if sertraline was listed under restrictions similar to mirtazapine (i.e. third line) it would displace at least 10% of the use of currently funded SSRIs and approximately 20% of venlafaxine use. Members noted that it was simpler to use than venlafaxine and has fewer side effects.

4.8 The Subcommittee considered that it was unlikely that patients taking sertraline would be on treatment for any less time than any other SSRI, noting that if it was more efficacious there was a possibility that patients would stay on it longer.

4.9 The Subcommittee reiterated its previous recommendation to list sertraline without restrictions only if it was cost-neutral to the Pharmaceutical Budget.

4.10 However, because of the potential for savings from reduced use of venlafaxine, the Subcommittee **recommended** that sertraline be funded subject to restrictions similar to those recommended for mirtazapine. The Subcommittee considered that, within the context of the mental health therapeutic area, this recommendation should be considered a high priority.

4.11 The Decision Criteria particularly relevant to these recommendations 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.*

5 Venlafaxine immediate-release tablets

5.1 The Subcommittee noted that PHARMAC staff had received queries from suppliers about the possibility of listing venlafaxine immediate-release (IR) tablets in the Pharmaceutical Schedule and were seeking advice from the Subcommittee to inform their actions around this product.

5.2 The Subcommittee reviewed a study comparing venlafaxine IR with venlafaxine extended-release (XR) in outpatients with major depression (Cunningham et al, Annal Clin Psychiatry 1997;9(3):157-164). The Subcommittee noted that the XR preparation was superior to the IR preparation at weeks 8 and 12 on the primary outcome measure; however, members noted that patients on the IR formulation were taking a lower dose than patients on the XR formulation.

5.3 The Subcommittee considered that it was reasonable to assume that any efficacy benefits of the XR preparation (e.g., efficacy in treatment-resistant depression) would also extend to the IR preparation at equivalent doses.

5.4 The Subcommittee considered that the key differences between the two formulations related to their different side effect profiles: in particular, the XR preparation is associated with more urinary retention and sexual dysfunction in men whereas the IR preparation is associated with more early onset nausea. Members noted that it was, in theory, possible to administer the IR preparation once daily and still receive the same efficacy benefit, but the impact of nausea was reduced by twice-daily administration. The Subcommittee considered that the nausea from the IR presentation would become intolerable for many patients at doses of 150 mg per day and above.

5.5 The Subcommittee considered that availability of venlafaxine IR would be clinically useful in patients on doses below 150 mg per day venlafaxine who wished to avoid the side effects of the XR preparation, in particular the sexual dysfunction.

5.6 The Subcommittee considered that if venlafaxine IR was funded it would be useful to provide some educational information about the relative benefits of the IR preparation compared with the XR preparation.

5.7 The Subcommittee considered that it would not be clinically appropriate for venlafaxine to be funded as a first-line treatment option for depression and, therefore, **recommended** that if venlafaxine IR was listed in the Pharmaceutical Schedule it should be subject to the same or similar restrictions as the XR preparation.

5.8 The Subcommittee considered that if venlafaxine IR was listed under these criteria approximately 10% of patients would switch from venlafaxine XR, which could represent significant savings (depending on the price of venlafaxine IR). For this reason, the Subcommittee **recommended** funding venlafaxine IR, under restrictions as proposed. The Subcommittee considered that, within the context of the mental health therapeutic area, this recommendation should be considered a high priority.

5.9 The Decision Criteria particularly relevant to these recommendations 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.*

6 Olanzapine depot injection (Zyprexa Relprevv)

6.1 The Subcommittee reviewed an application from Eli Lilly for funding of olanzapine depot injection (Zyprexa Relprevv) for the treatment of patients with schizophrenia and related disorders who have tried but been unable to comply with treatment using oral antipsychotic agents and who have been admitted to hospital or treated in respite care, or intensive outpatient or home-based treatment, for 30 days or more in the last 12 months.

6.2 The Subcommittee noted that PTAC had reviewed the application in May 2009 and had recommended that the application for funding of olanzapine depot injection be deferred pending a cost-utility analysis being performed by PHARMAC staff and a review of the application by the Mental Health Subcommittee.

6.3 The Subcommittee noted that, in addition to the funding application submitted to PHARMAC, the supplier had also sent a separate letter to each Subcommittee member in relation to the application, which members felt was inappropriate.

6.4 The Subcommittee noted that olanzapine depot injection is only registered for use in adults and that the Medsafe datasheet states that it has not been studied in patients under 18 years of age. Members considered that it would be useful for studies to be conducted in adolescent patients, given that it is not uncommon for the onset of schizophrenia to occur between the ages of 13 and 17 years.

6.5 The Subcommittee considered that the evidence provided by the supplier was of good quality, although only one of the placebo-controlled trials appeared to be published (Lauriello et al, J Clin Psychiatry 2008;69:790-799). The Subcommittee noted that approximately two-thirds of patients on depot antipsychotic treatment in New Zealand receive depot antipsychotics as part of a Compulsory Treatment Order. In this respect, the Subcommittee considered that the study populations were not completely representative of the New Zealand population.

6.6 The Subcommittee considered that the evidence supported a benefit of olanzapine depot injection over placebo in acutely ill patients with schizophrenia and that the depot injection provides similar efficacy to olanzapine tablets in the maintenance treatment of schizophrenia.

6.7 The Subcommittee noted that the studies identified no new adverse events with olanzapine. However, members noted that olanzapine depot injection was associated with injection-related overdose in a small proportion of patients (less than 1%), which required admission to hospital in 79% of cases. The Subcommittee considered that this was a potentially significant issue and would probably mean that patients receiving olanzapine depot would need to be monitored for up to three hours for the signs and symptoms of overdose (including sedation, delirium and/or extrapyramidal symptoms). The Subcommittee considered that this should be factored into any cost-utility analysis, noting that if a family member or caregiver was not available to monitor patients they may need to have the treatment administered in hospital.

6.8 The Subcommittee noted that there were no studies directly comparing olanzapine depot injection with risperidone depot injection, which was relevant given that risperidone depot injection is now the most widely used depot antipsychotic in New Zealand.

6.9 The Subcommittee considered that there were currently no particular problems with access to antipsychotic depot preparations. However, the Subcommittee considered that there was a need for another option for patients with schizophrenia and Parkinson's disease or severe extrapyramidal side effects from other antipsychotic medications and who were non-compliant with oral antipsychotic medication, as the current options were not suitable for these patients.

6.10 The Subcommittee considered that there was no direct evidence to suggest that olanzapine depot injection would be associated with lower discontinuation rates than risperidone depot injection in clinical practice.

6.11 The Subcommittee considered that the key differences between risperidone depot injection and olanzapine depot injection related to the side effect profiles of the two products, with data suggesting that olanzapine depot injection is associated with less extrapyramidal side effects and sexual dysfunction than risperidone depot injection.

6.12 However, the Subcommittee noted that olanzapine depot injection is associated with clinically significant weight gain. Members considered that this would affect Maori and Pacific peoples to a greater extent as they have higher rates of compulsory admission and treatment with antipsychotic depot preparations and are more susceptible to weight gain.

6.13 The Subcommittee noted that olanzapine depot injection could be given monthly, which would be an advantage over fortnightly risperidone depot injections.

6.14 The Subcommittee considered that, given the increased risk of metabolic problems in a patient group particularly vulnerable to such problems, it would be clinically appropriate to require a trial of oral risperidone prior to accessing funded olanzapine depot injection. The Subcommittee considered that it was possible that patients who were non-compliant on oral olanzapine might become compliant on oral risperidone because of the differences in side effect profiles.

6.15 The Subcommittee considered that approximately half of new patients would be initiated on olanzapine depot injection instead of risperidone depot injection if they were both funded under similar access criteria, although the proportion of patients initiated on olanzapine depot injection could be greater depending on the relative marketing of the two products. The Subcommittee further considered that the availability of olanzapine depot injection could further displace use of older-generation antipsychotic depot injections and could potentially increase the overall antipsychotic depot injection market. The Subcommittee agreed with PTAC's view that the extent of market uptake of olanzapine depot injection had been underestimated by the supplier. For these reasons, the Subcommittee considered that there would be a significant fiscal risk if olanzapine depot injection was funded under the same criteria as risperidone depot injection.

6.16 The Subcommittee **recommended** that olanzapine depot injection be funded subject to similar Special Authority restrictions to risperidone depot injection, but with the added requirement for a trial of oral risperidone. The Subcommittee considered that, within the context of the mental health therapeutic area, this recommendation should be considered a medium-high priority.

6.17 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.*

7 Olanzapine wafers (Zyprexa Zydis)

7.1 The Subcommittee reviewed an application from a clinician to widen access to olanzapine wafers to allow their use as an alternative to the tablets (i.e. subject to the same restrictions as the tablets) because of evidence to suggest that the wafers are associated with less weight gain.

7.2 The Subcommittee considered that the strength of the evidence was weak, in that the studies were conducted in small numbers of patients, were short-term, and only one was randomised (de Haan et al, Psychopharmacology 2004;175:389-390).

7.3 The Subcommittee also noted that most of the studies were several years old; members considered that if the benefits had been real and sustained over the longer term this would have emerged in subsequent studies, which did not appear to be the case.

7.4 [withheld under s9(2)(j) of the OIA

7.5 The Subcommittee considered that the evidence for a benefit of olanzapine wafers over the tablets in terms of weight gain was not compelling enough to alter access to the wafers given the longer-term financial risk associated with such a change. Therefore, the Subcommittee **recommended** that the application to widen access to olanzapine wafers be declined.

7.6 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; (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.*