

PTAC meeting held 7 & 8 May 2009

(minutes for web publishing)

PTAC 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 PTAC meeting; only the relevant portions of the minutes relating to PTAC discussions about an application that contain a recommendation are published.

PTAC 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 protect the privacy of natural persons (section 9(2)(a)).

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1 Minutes of PTAC Meeting Held 19 & 20 February 2009

1.1 The Committee reviewed the minutes of the PTAC meeting held on 19 & 20 February 2009 and **recommended** the following minor amendments:

1.1.1 Enzyme Replacement Therapies: replace “Schieie” with “Scheie”.

1.1.2 Enzyme Replacement Therapies: paragraph 6.1: replace “The Committee considered an application from PHARMAC staff” with “The Committee considered a proposal from PHARMAC staff”.

2 Losartan Special Authority

Application

2.1 The Committee reviewed an application from AstraZeneca, which included an independent report from, [withheld under s9(2)(a) of the OIA] requesting that the “unsatisfactory response to an ACE inhibitor” criteria in the losartan Special Authority is amended so that combination therapy (losartan plus an ACE inhibitor) is not funded for:

2.1.1 heart failure (AstraZeneca’s request)

2.1.2 any patients ([withheld under s9(2)(a) of the OIA]’s request)

Recommendation

2.2 The Committee **recommended** that the application be declined.

2.3 The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals.*

2.4 The Committee **recommended** that a warning should be added to the Losartan Special Authority, noting that combination therapy should only be used when strictly necessary in individual patients and that these patients should be carefully monitored for adverse events.

2.5 The Committee **recommended** that prescriber education should be undertaken, and that PHARMAC should write to [withheld under s9(2)(a) of the OIA] suggesting that an article noting the risks of combination therapy, with an ACE inhibitor and angiotensin receptor blocker should be written for Prescriber Update.

Discussion

2.6 The Committee noted recent evidence regarding the combination use of ACE inhibitors and ARB’s including Yusuf et al (N Engl J Med 358: 1547-59, 2008), Mann et al (Lancet

372: 547-53, 2008), Messerli, F. H. (J Am Coll Cardiol 53: 468-70, 2009), and Titan et al (Presentation at the American Society of Nephrology Conference, Nov 2008), which suggested that there was no additional benefit of combining an ARB with an ACEI over an ACEI alone and that combination therapy may result in an increase in adverse events.

- 2.7 The Committee reviewed the evidence for combination therapy in heart failure and hypertension.
- 2.8 The Committee noted that some renal clinicians considered that there was a place for combination therapy in a small group of patients, outside of the majority patient population included in the ONTARGET trial, while others did not.
- 2.9 The Committee noted that the majority of Special Authority approvals under the “unsatisfactory response to an ACE inhibitor” criteria were from General Practitioners.
- 2.10 The Committee noted that the Special Authority criteria were not specific to any indication, similar to a number of other Special Authority criteria listed in the Pharmaceutical Schedule, and that prescribers should take responsibility for appropriate clinical prescribing. The Committee considered that General Practitioners are unlikely to be aware of the latest evidence regarding the safety of combination ACE inhibitor and ARB therapy and discussed whether combination therapy should be a specialist only treatment.
- 2.11 The Committee concluded that there may be a place for combination therapy in a small number of individual patients, but that given the latest evidence regarding combination therapy and the likelihood that prescribers may not be aware of this evidence, that it would be appropriate for a warning to be added to the current losartan Special Authority. In addition the Committee concluded that it would be appropriate for an article on the risks of combination therapy to be included in the Prescriber Update.

3 Olanzapine depot injection (Zyprexa Adhera) for schizophrenia and related disorders

Application

- 3.1 The Committee reviewed an application from Eli Lilly NZ Ltd for the listing of olanzapine depot injection (Zyprexa Adhera) on the Pharmaceutical Schedule 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.

Recommendation

- 3.2 The Committee **deferred** making a recommendation on the application for olanzapine depot injection pending a cost-utility analysis being performed by PHARMAC staff and a review of the application by the Mental Health Subcommittee.

Discussion

- 3.3 The Committee noted that the goal of depot antipsychotic treatment is to reduce the severity and frequency of relapse by improving compliance.
- 3.4 The Committee noted that depot antipsychotic treatment in New Zealand is generally used as part of a Compulsory Treatment Order (CTO) and that not many patients are receiving ongoing depot antipsychotic treatment by choice.
- 3.5 The Committee noted that Maori and Pacific peoples have higher rates of compulsory admission and treatment. It further noted that they have higher rates of non-compliance, and that the excess burden for the Maori and Pacific populations from refractory psychoses might better be improved by dedicated Maori mental health services than by the addition of newer depot antipsychotic agents.
- 3.6 The Committee noted that risperidone depot injection is now the preferred first-choice depot antipsychotic, although many patients remain on older agents where they are stabilised on treatment or reluctant to change.
- 3.7 The Committee noted that olanzapine tablets have been funded for several years in New Zealand and are considered to be a first-line treatment for schizophrenia.
- 3.8 The Committee considered that the evidence provided by the supplier was of good quality, with well-designed trials with appropriate outcome measures and reasonable retention rates, although only one of the placebo-controlled trials appeared to be published (Lauriello et al, J Clin Psychiatry 2008;69:790-9). The Committee considered that the study populations were not completely representative of the New Zealand population, but noted that it was not possible to conduct clinical trials on patients with a CTO.
- 3.9 The Committee considered that the evidence supported a benefit of olanzapine depot injection over placebo in acutely ill patients with schizophrenia and that olanzapine depot injection is non-inferior to olanzapine tablets in the maintenance treatment of schizophrenia.
- 3.10 The Committee noted that the studies identified no new adverse events with olanzapine; however, olanzapine depot injection was associated with injection-related overdose in a small proportion of patients (less than 1%). Symptoms of acute overdose following olanzapine injection included sedation, delirium and/or extrapyramidal symptoms; none were fatal and all resolved within 24 hours, but in most cases the patients were admitted to hospital. The Committee considered that this was a significant issue, although the impact in clinical practice remains uncertain.
- 3.11 The Committee noted that there were no direct comparisons of olanzapine depot injection with risperidone depot injections. However, the Committee considered that indirect comparisons suggest that the efficacy of the two treatments would be comparable, with the key differences likely to be in the side effect profiles (similar to that seen with the oral preparations of the two agents; i.e., more extrapyramidal side effects with risperidone and more weight gain with olanzapine). The Committee considered that

because of the way depot antipsychotics were used in New Zealand (i.e., mostly as part of a CTO) it would be difficult to argue that a new depot antipsychotic would improve compliance and, hence, reduce relapse rates.

- 3.12 The Committee considered that the dose of olanzapine depot injection would be approximately equivalent to oral olanzapine.
- 3.13 The Committee considered that there was a need for a depot injection antipsychotic that was associated with less extrapyramidal side effects and the prolactin-related problems that can be significant with the existing treatment options.
- 3.14 The Committee considered that if olanzapine depot injection was funded, there would be further growth in the number of patients on depot injections, and ultimately there would likely be a shift from the older agents towards risperidone and olanzapine depot injections. The Committee considered that the extent of market uptake of olanzapine depot injection had been underestimated by the supplier.
- 3.15 The Committee considered that olanzapine depot injection would have the biggest impact on the risperidone depot injection market. The Committee noted that olanzapine depot injection could be given monthly, which it considered would be an advantage over fortnightly risperidone depot injections.
- 3.16 The Committee noted that the supplier had not performed a cost-utility analysis, and considered that this would be an important piece of information to inform a funding decision. The Committee considered that the key comparators for the analysis would be oral olanzapine and risperidone depot injection.

4 Paliperidone (Invega) for schizophrenia and related psychoses

Application

- 4.1 The Committee reviewed an application from Janssen-Cilag Pty Ltd for the listing of paliperidone (Invega) tablets on the Pharmaceutical Schedule for the treatment of patients with schizophrenia and related psychoses in whom an effective dose of risperidone or quetiapine has been trialled and has been discontinued (or is in the process of being discontinued) because of unacceptable side effects or because of inadequate clinical response.

Recommendation

- 4.2 The Committee considered that there was no clinical reason not to list paliperidone; however, given the relative lack of evidence of benefits over currently funded treatments, in particular risperidone, the Committee **recommended** that paliperidone only be listed on the Pharmaceutical Schedule if it was no more expensive than risperidone.
- 4.3 The Decision Criteria 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.

Discussion

- 4.4 The Committee noted that paliperidone is the major active metabolite of risperidone (9-hydroxyrisperidone) and that it undergoes minimal hepatic metabolism.
- 4.5 The Committee considered that the supplier had provided good quality evidence demonstrating the superior efficacy of paliperidone over placebo in the treatment of schizophrenia. The Committee noted that the main evidence was from three 6-week, randomised, double-blind trials comparing paliperidone with placebo and with olanzapine (Kane et al, *Schizophr Res* 2007;90:147-61; Marder et al, *Biol Psychiatry* 2007;62:1363-70; Davidson et al, *Schizophr Res* 2007;93:117-30), and from a 24-week randomized placebo-controlled recurrence trial (Kramer et al, *J Clin Psychopharmacol* 2007;27:6-14).
- 4.6 The Committee considered that the evidence supporting a benefit of paliperidone over other antipsychotics was limited. The Committee considered that the comparison of paliperidone with olanzapine in the above mentioned randomized placebo-controlled, active-controlled trials was questionable, as the dose of olanzapine used in the studies was relatively low and paliperidone only appeared to provide similar benefit to olanzapine at the higher doses of paliperidone. However, the Committee noted that paliperidone was associated with less weight gain than olanzapine. The Committee noted that one short-term (6-week) randomized, double-blind trial comparing paliperidone (9–12 mg) with quetiapine (600–800 mg) showed an efficacy benefit for paliperidone over quetiapine in terms of improvements in mean Positive and Negative Syndrome Scale (PANSS) total change score (Canuso et al, *Am J Psychiatry* 2009;May 1[Epub ahead of print]).
- 4.7 The Committee considered that of the currently funded treatments, paliperidone would be most similar to risperidone, given its chemical structure. As such, the Committee considered that the most appropriate comparator treatment in the New Zealand market is risperidone; however, the Committee noted that the supplier had not provided any published studies comparing either the effectiveness or tolerability of paliperidone with risperidone.
- 4.8 The Committee noted the post-hoc subgroup analysis of paliperidone in patients who had previously tried risperidone (Canuso et al, *Int Clin Psychopharmacol* 2008;23:209-15). The Committee considered that the effectiveness of paliperidone in patients who had previously tried risperidone was uncertain, given that the dose equivalence of paliperidone and risperidone was unclear. The Committee noted that patients who had previously tried risperidone (mean dose approximately 4 mg per day) who responded better to higher doses of paliperidone (6–12 mg per day) than to placebo may have also responded better to similarly high doses of risperidone.
- 4.9 The Committee considered that the evidence suggested that paliperidone was relatively well tolerated, with common side effects being weight gain, tachycardia, elevated prolactin and extrapyramidal side effects.

- 4.10 The Committee noted that a key benefit for paliperidone claimed by the supplier is once-daily dosing; however, the Committee noted that there are several funded antipsychotics that can be given once daily, including aripiprazole, risperidone, olanzapine and amisulpride at higher doses.
- 4.11 The Committee considered that there was no particular unmet clinical need that would be met by funding paliperidone, although members considered there could be a niche role for paliperidone in patients with hepatic impairment.
- 4.12 The Committee noted that there was no evidence presented to suggest that use of paliperidone would reduce healthcare expenditure (e.g., due to reductions in hospitalisations, reduced use of depot antipsychotics, or reductions in management of antipsychotic-related metabolic problems).
- 4.13 The Committee considered that there was no clinical reason to place any restrictions on paliperidone, and that any such restrictions would be for financial reasons. The Committee considered that both the market share and the dose of paliperidone had been underestimated by the supplier. The Committee considered it likely that doses greater than 10 mg per day would be used, particularly given the proposed restriction limiting its use to second-line treatment.

5 Octreotide for Multiple Indications

- 5.1 The Committee considered applications for the funding of octreotide for the treatment of patients with malignant bowel obstruction, TSH-producing pituitary adenomas or acromegaly. Each of these applications was discussed separately.
- 5.2 The Committee noted a mistake in the current Special Authority criteria for octreotide, specifically that criterion 5 “For pre-operative control of hypoglycaemia and for maintenance therapy; or” should be part of the criteria for Insulinoma’s, 4, 4.1 and 4.2. The Committee **recommended** renumbering this criterion 4.3.

(A) Malignant Bowel Obstruction

Application

- 5.3 The Committee considered an applications from the Hospital Exceptional Circumstances (HEC) Panel, the Ministry of Health’s Palliative Care Medications Working Group (PCMWG) and a proposal from PHARMAC staff to amend the Special Authority for octreotide in the Pharmaceutical Schedule to include the treatment of nausea and vomiting in patients (who are usually terminally ill) with malignant bowel obstruction unresponsive to first line treatment with anti-muscarinic agents, corticosteroids and antiemetics.

Recommendation

- 5.4 The Committee **recommended** that the Special Authority for octreotide should be widened to include second line treatment of malignant bowel obstruction. The Committee **recommended** restricting funding to short term treatment (two to three weeks) with 300-600µg daily octreotide where treatment with antiemetics, rehydration, antimuscarinic agents, corticosteroids and analgesics for five days had failed; the Committee gave this recommendation a high priority. Members **recommended** that additional (> 3 weeks) treatment could be considered where the patient is benefiting from treatment.
- 5.5 The Committee **recommended** that the PCMWG provide a protocol for the management of patients with malignant bowel obstruction.
- 5.6 The Decision Criteria 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.*

Discussion

- 5.7 The Committee noted that the application had been reviewed by the Analgesic Subcommittee of PTAC at its March 2009 meeting and that the Subcommittee recommended that funded access to octreotide be widened to include management of nausea and vomiting in patients with malignant bowel obstruction unresponsive to first-line treatment with anti-muscarinic agents, steroids and antiemetics, with a high priority.
- 5.8 The Committee noted that this was not a registered indication for octreotide and that it was not funded for this indication in Australia.
- 5.9 The Committee noted that HEC received about 15 applications per year for octreotide for this indication, almost all of which were approved. The Committee noted, however, that the Analgesic Subcommittee of PTAC considered up to 60 patients per year would access treatment if funded. The Committee considered this estimate to be accurate given that the majority of these patients would likely be in a hospice setting rather than in hospital and would therefore not be picked up through HEC applications. Members noted that neither HEC nor discretionary community supply listings are appropriate for patients in a hospice setting.
- 5.10 The Committee noted that there was a high level of unmet clinical need in patients who have not responded to first-line treatment with antiemetics, rehydration, antimuscarinic agents, corticosteroids and analgesics for five days. The Committee noted that prognosis in these patients was very poor, for example the mean survival time in one trial was only 11.6 days (Ripamonti et al, Journal of Pain and Symptom Management 2000; 19: 23-34).
- 5.11 The Committee reviewed a literature search provided by PHARMAC staff. The Committee noted that there were numerous small studies, but no good large randomised controlled studies in this setting. Members considered that these studies demonstrated octreotide may be effective at reducing symptoms (nausea, vomiting, secretions and pain) in some patients who have not responded to antimuscarinics.
- 5.12 The Committee considered that since treatment in this setting would be short, two to three weeks, at a dose of 300-600µg octreotide daily, the short acting preparation of octreotide would be used and it would not be necessary to fund the long acting preparation, octreotide-LAR.

(B) TSH-producing pituitary tumours

Application

5.13 The Committee reconsidered an application from a clinician requesting that the Special Authority criteria for octreotide be widened to include the treatment of patients with thyrotropin (TSH)-secreting pituitary adenomas. The Committee also reviewed a literature search provided by PHARMAC staff.

Recommendation

5.14 The Committee reiterated its November 2008 recommendation that octreotide for TSH producing pituitary adenomas should continue to be considered under Exceptional Circumstances because this was a rare condition.

5.15 The Decision Criteria 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.*

Discussion

5.16 The Committee noted that the treatment of patients with thyrotropin (TSH)-secreting pituitary adenomas was not a registered indication for octreotide and there were no randomised clinical trails in this setting.

5.17 The Committee considered that although octreotide, post surgery, was associated with biochemical control of hyperthyroidism in most patients and tumour shrinkage in some patients, there was no evidence that this improved cure rates.

5.18 The Committee considered that patients who have not achieved biochemical control after surgery and radiotherapy, or where radiotherapy is contraindicated may benefit from octreotide treatment. Members noted that the effects of radiotherapy may not be apparent for some time (months/years). The Committee considered that there was no data to support the use of octreotide pre-surgery.

(C) Acromegaly

Application

5.19 The Committee reconsidered applications from clinicians requesting that the Special Authority criteria for octreotide be widened to include treatment of patients with acromegaly who are unsuitable for surgery and for pre-surgical treatment of acromegaly. The Committee also reviewed a literature search provided by PHARMAC staff.

Recommendation – Pre-surgery treatment of acromegaly

5.20 The Committee **recommended** that the applications for pre-surgical treatment of acromegaly should continue to be considered under Exceptional Circumstances.

5.21 Decision Criteria 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.*

Discussion – Pre-surgery treatment of acromegaly

5.22 The Committee noted that this was not a registered indication for octreotide and there were no persuasive randomised clinical trials in this setting.

5.23 The Committee noted that most studies were small, observational, short term and used surrogate markers of surgical cure, mainly IGF1 levels. Members noted that improvements in IGF1 levels and short-term surgical cure rates were apparent in some studies but not others.

5.24 The Committee considered that in some studies octreotide was associated with some tumour shrinkage and/or tumour softening, however there was no good evidence that this, rather than other factors such as surgical skill, improved surgical cure rates. Members noted that there was no data on long-term cure rates or survival rates.

5.25 The Committee considered that there was inadequate evidence to demonstrate that pre-surgical treatment with octreotide improved long-term outcomes in patients with acromegaly.

Recommendation – Treatment of acromegaly in patients for whom surgery is contraindicated

5.26 The Committee **recommended** that the Special Authority criterion for octreotide use in acromegaly be amended as follows (changes shown in bold and strikethrough)

Special Authority for Subsidy

Initial application only from a relevant specialist. Approvals valid for ~~2 years~~ **3 months** for applications meeting the following criteria:

Any of the following:

1 Both:

1.1 Acromegaly; and

1.2 Any of the following:

1.2.1 Patient has failed surgery, radiotherapy, ~~bromocriptine and other oral therapies~~ dopamine agonists; or

1.2.2 Treatment for an interim period while awaiting the effects of radiotherapy and dopamine agonists have failed; or

1.2.3 Patient is unwilling, or unable, to undergo surgery and radiotherapy is contraindicated.

Renewal – (Acromegaly) only from a relevant specialist. Approvals valid for 2 years ~~where the treatment remains appropriate and the patient is benefiting from treatment for~~ **applications meeting the following criteria:**

1 Both:

1.1 IGF1 levels have decreased since starting octreotide; and

1.2 the treatment remains appropriate and the patient is benefiting from treatment.

Note: Octreotide treatment should be discontinued if IGF1 levels have not decreased after 3 months treatment . In patients treated with radiotherapy octreotide treatment should be withdrawn every 2 years, for 1 month, for assessment of remission.

Octreotide treatment should be stopped where there is biochemical evidence of remission (normal IGF1 levels) following octreotide treatment withdrawal for at least 4 weeks.

- 5.27 The Committee gave this recommendation a **medium** priority.
- 5.28 Decision Criteria 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.*

Discussion – Treatment of acromegaly in patients for whom surgery is contraindicated

- 5.29 The Committee noted that octreotide is indicated for symptomatic control and reduction of growth hormone (GH) and IGF-1 plasma levels in patients with acromegaly who are inadequately controlled by surgery or radiotherapy. Members further noted that it is also indicated for acromegalic patients unfit or unwilling to undergo surgery, or in the interim period until radiotherapy becomes fully effective.
- 5.30 The Committee noted that currently octreotide is only funded for acromegalic patients where treatment with surgery, radiotherapy, bromocriptine and other therapies have failed. The Committee re-iterated its previous recommendation that the only relevant oral therapy funded on the Pharmaceutical Schedule would be bromocriptine, therefore the phrase ‘and other oral therapies’ could be removed from the Special Authority criteria.
- 5.31 The Committee considered that it would be appropriate to amend the Special Authority to be in line with the registered indication and the Australian PBS listing. The Committee considered that amending the Special Authority thus would not result in many additional patients accessing funded treatment. Members noted that only four EC applications for acromegaly had been received since July 2005.
- 5.32 The Committee considered that since treatment in this setting was long term it would be necessary to fund the long acting preparation, octreotide-LAR.

6 Musculoskeletal Pharmaceutical Subsidies

(A) Non-steroidal anti-inflammatory drug (NSAID) subsidies

Application

- 6.1 The Committee considered an application from the Palliative Care Medications Working Group (a Subcommittee of the Palliative Care Working Party) to amend the Special Authority for manufacturer’s price for part-funded NSAIDs in the Pharmaceutical Schedule to include the treatment of bone pain or inflammatory conditions in palliative care and patients unable to take tablet formulations due to swallowing difficulties or requiring gastrostomy feeding.

Recommendation

- 6.2 The Committee **recommended** that the Application from the Palliative Care Medications Working Group be declined due to lack of evidence.
- 6.3 The Committee further **recommended** that the Special Authority for manufacturer's price for part-funded NSAIDs should not be removed unless all presentations of ibuprofen were fully funded. The Committee further **recommended** that if all presentations of ibuprofen were fully funded, the Special Authority should be removed; however, the Committee noted that this would result in several NSAID preparations incurring a part charge and, therefore, PHARMAC would need to give due consideration to implementation issues. The Committee gave the second recommendation a medium priority.
- 6.4 The Decision Criteria relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (vii) The direct cost to health service users.*

Discussion

- 6.5 The Committee noted that the Special Authority for manufacturer's price for partially funded NSAID presentations (diclofenac sodium tab 50 mg dispersible; ibuprofen tab 400 mg and 600 mg and tab long-acting 800 mg; ketoprofen cap long-acting 100 mg and 200 mg; mefenamic acid cap 250 mg; sulindac tab 100 mg and 200 mg; and tiaprofenic acid tab 30 mg) is limited to patients with inflammatory arthritis who are stabilised and well controlled on the particular NSAID medication.
- 6.6 The Committee noted that it had previously recommended removing the Special Authority for manufacturer's price for partially funded NSAIDs, and that this would result in the abovementioned NSAID presentations incurring a part charge.
- 6.7 The Committee noted that approximately 80% of the ~1,500 current Special Authority approvals are being used for ibuprofen formulations, and 96% of those are for the tab long-acting 800 mg formulation. The Committee noted that PHARMAC staff intended to recommend fully funding ibuprofen tab 400 mg and 600 mg and tab long-acting 800 mg via the annual tender.
- 6.8 The Committee noted that fewer than 10 patients were currently accessing full subsidy for diclofenac sodium tab 50 mg dispersible via Special Authority; however, if the Special Authority was removed and the presentation fully funded the cost to the Pharmaceutical Budget would be substantially greater and would need to be prioritised accordingly against other possible expenditure options.
- 6.9 The Committee noted that the applicant had provided two review articles indicating that NSAIDs are useful for cancer pain and are step one on the World Health Organisation's three-step "ladder" for cancer pain relief. The Committee noted that no evidence had been provided in support of any particular NSAID.

- 6.10 The Committee considered that there were sufficient fully funded NSAID options for palliative care patients, including ibuprofen oral liquid, and that no evidence had been provided that would justify a change to the Special Authority criteria.

(B) Baclofen

Application

- 6.11 The Committee considered an application from the Palliative Care Medications Working Group (a Subcommittee of the Palliative Care Working Party) to list baclofen injection on the Pharmaceutical Schedule for intrathecal and injectable use in palliative care.

Recommendation

- 6.12 The Committee **recommended** that the Application from the Palliative Care Medications Working Group be declined due to lack of evidence.
- 6.13 The Committee further **recommended** that baclofen injection be included on the Discretionary Community Supply (DCS) list, restricted to patients with severe chronic spasticity of cerebral origin or due to multiple sclerosis, spinal cord injury or spinal cord disease, where oral antispastic agents have failed or have caused unacceptable side effects.

Discussion

- 6.14 The Committee noted that the Palliative Care Medications Working Group had not provided any evidence in support of its Application.
- 6.15 The Committee noted that the baclofen Medsafe datasheet specifically excludes administration of baclofen injection outside the cerebrospinal fluid. Therefore, the Committee limited its discussion to consideration of intrathecal baclofen according to its registered indications.
- 6.16 The Committee noted that baclofen intrathecal injection 10 mg in 5 mL was mainly used in a programmable pump. The Committee considered that there are considerable safety risks associated with this use of baclofen, including the risk of fatalities and withdrawal syndrome related to pump malfunction or failure to provide refill doses. The Committee noted that insertion of the pump is a neurosurgical procedure. Because of this, the Committee considered that it would not be appropriate to fund baclofen injection in the community.
- 6.17 The Committee noted that funding of baclofen injection in Australia is restricted to patients with severe chronic spasticity of cerebral origin or due to multiple sclerosis, spinal cord injury or spinal cord disease, where oral antispastic agents have failed or have caused unacceptable side effects. The Committee considered that these restrictions would be appropriate if baclofen injection was funded in New Zealand.

- 6.18 The Committee noted that it would be willing to re-review baclofen injection if the Palliative Care Medications Working Group was able to provide published clinical trial data in support of the use of baclofen injection for other indications.

7 Buprenorphine transdermal patch (Norspan) for the treatment of moderate-to-severe pain

Application

- 7.1 The Committee reviewed a re-application from Mundipharma New Zealand Ltd for the listing of buprenorphine transdermal patches (Norspan) on the Pharmaceutical Schedule for the treatment of moderate-to-severe pain.

Recommendation

- 7.2 The Committee **recommended** that buprenorphine transdermal patches be listed in the Pharmaceutical Schedule, subject to Special Authority criteria restricting its use to patients who have not responded to other opioid analgesics, with a low priority.
- 7.3 The Decision Criteria 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.*

Discussion

- 7.4 The Committee noted that it had previously recommended that the initial application to list buprenorphine transdermal patches on the Pharmaceutical Schedule for the treatment of moderate-to-severe pain be declined, taking into account the lack of longer-term studies and post-marketing surveillance data, the relative lack of studies versus funded comparator treatments and the lack of unmet clinical need.
- 7.5 The Committee noted that the applicant had now provided additional information to address some of the points raised by the Committee in the initial review of the Application.
- 7.6 After reviewing the information provided by the applicant, the Committee revised its estimate of the relative potency of buprenorphine patches to 60:1 compared with oral morphine. This means that a 5 mg buprenorphine patch would be roughly equivalent to 7.2 mg of oral morphine, 72 mg of codeine and DHC, 36 mg of oral tramadol, and 3.6 mg of oral oxycodone, all over a 24 hour period.
- 7.7 The Committee noted that the applicant's estimate of an 18.5% point prevalence of chronic pain was derived from a telephone survey of households in New South Wales, Australia, with chronic pain defined as pain experienced every day for three months in

the six months prior to the interview. The Committee considered that this methodology was not very robust, and considered that the point prevalence of chronic pain was likely to be considerably lower than 18.5%.

- 7.8 The Committee considered that the new evidence provided by the applicant supported the safety of buprenorphine transdermal patches in patients with impaired renal function (Filitz et al, Eur J Pain 2006;10:743-8), but there did not appear to be a particular safety advantage for buprenorphine in patients with liver impairment.
- 7.9 The Committee considered the applicant's claim of a differential effect of buprenorphine on analgesia compared with respiratory depression. The Committee noted that while there is some support for this from the experimental studies offered in the reapplication which was consistent with buprenorphine being a partial agonist at the μ receptor there was no clinical evidence offered to support this in chronic pain patients.
- 7.10 The Committee considered that the evidence provided in support of a niche role for buprenorphine transdermal patches in the elderly on the basis of reduced risk of falls and fractures compared with other opioids was weak. The Committee noted that the Medsafe datasheet lists side effects of dizziness, somnolence and confusion as very common (>10%); therefore, the Committee considered that it would be prudent to exercise caution in treating frail ambulant elderly patients with buprenorphine transdermal patches.
- 7.11 The Committee noted the applicant's submission that, due to its actions as a partial agonist at the mu opioid receptor, buprenorphine transdermal patches has a unique place in therapy ahead of full agonists; however, the Committee questioned the clinical relevance of this.
- 7.12 The Committee considered that the applicant's claim of reduced risk of physical dependence is largely theoretical, related to the pharmacodynamic properties of buprenorphine. The Committee noted that there do not appear to be any withdrawal studies in the chronic pain setting, although an abstinence syndrome is described, which begins two days after patch removal and lasts as long as two weeks.
- 7.13 Similarly, the Committee considered that the new evidence provided by the supplier in support of low abuse potential with buprenorphine patches was not strong, although members considered that buprenorphine patches would likely have less potential for abuse than existing funded opioids (e.g., morphine) used in low doses for chronic pain.
- 7.14 The Committee noted that it had previously raised concerns that the patch could result in skin tearing and reactions in elderly patients with papery skin. The Committee noted that skin exfoliation on patch removal had been monitored by the Australian pharmacovigilance database, which shows that while skin reactions are very common (approximately 15%) actual skin loss is rare (<1%).
- 7.15 The Committee noted that the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia had recommended funding of buprenorphine patches on the strength of a cost minimisation comparison with long-acting oxycodone. However, the PBAC had also noted that buprenorphine patches were not well established and more familiar opioids were available in a broader range of doses. The Committee noted that the Scottish

Medicines Consortium had recommended against funding buprenorphine patches in Scotland because the supplier had not presented a sufficiently robust economic analysis.

- 7.16 The Committee reviewed a study provided by the applicant comparing buprenorphine patches with sustained-release tramadol (Karlsson and Berggren, Clin Therapeutics 2009;31:503-13). The Committee considered that the results of this study supported the non-inferiority of buprenorphine patches to tramadol. The Committee noted that the study highlighted the probable need for prophylactic antiemetics for patients taking both treatments.
- 7.17 The Committee considered that tramadol was an appropriate comparator for buprenorphine transdermal patches; however, the Committee noted that as tramadol was not currently funded it would be necessary for any cost-benefit analysis to compare buprenorphine transdermal patches with currently funded low-dose opioids. The Committee considered that, in the context of budget impact and cost-benefit analyses it would be worthwhile to ask the applicant to provide the average daily dose of buprenorphine transdermal patches used in Australia as well as Australian usage data.
- 7.18 The Committee considered that the applicant had adequately addressed the Committee's key concerns.

8 Treatment of Multiple Class Resistant HIV Infection

- 8.1 The Committee reviewed a paper from PHARMAC staff regarding funding applications for raltegravir (Isentress, Merck Sharp and Dohme (New Zealand) Limited), darunavir (Prezista, Janssen-Cilag) and a proposed amendment of the current Special Authority criteria applying to antiretrovirals to allow more than three antiretrovirals to be used as optimised background therapy (OBT) in patients with multiple class resistant HIV infection.
- 8.2 The Committee considered there had been significant advances in antiretroviral therapy over the 18 months since PTAC initially considered the application for OBT. The Committee considered that the issue was no longer one of recycling old drugs with partial activity but the introduction of new treatments such as raltegravir and darunavir.

Recommendations

- 8.3 The Committee **recommended** that both raltegravir and darunavir be listed on the Pharmaceutical Schedule under Special Authority for the treatment of patients with multiclass drug resistant HIV infection as follows:

Special Authority for Subsidy

Initial application only from a named specialist. Approvals valid for six months for applications meeting the following criteria:

All of the following:

1 Confirmed HIV infection; and

2 Patient has evidence of HIV replication, despite ongoing therapy; and

3 Previous treatment with 2 different antiretroviral regimens has failed; and

- 4 HIV resistance testing and treatment history indicate multi class (ie NRTI, NNRTI and PI) resistance; and
- 5 treatment to be given in combination with least 1 antiretroviral drug that is fully active; and
- 6 A maximum of 5 antiretroviral agents can be used in the setting of multi-class resistance.

Renewal only from a named specialist. Approvals valid without further renewal unless notified where:

Both:

- 1 Evidence of maintaining an HIV viral load < 1000 copies per mL; and
- 2 The treatment remains appropriate and the patient is benefiting from treatment.

- 8.4 The Committee gave this recommendation a high priority. Members **recommended** that raltegravir and darunavir be listed at the same time as to ensure optimal usage.
- 8.5 The Decision Criteria 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 publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (vii) The direct cost to health service users.*

Discussion

- 8.6 The Committee noted that currently some 1100-1200 patients were taking antiretroviral therapy in New Zealand. Members considered that there was an unmet clinical need for patients who develop multiple drug resistance (MDR) to currently funded antiretroviral treatments. Members considered that 30 - 60 patients currently have MDR HIV and that another 5-10 new MDR patients would present each year. Members considered that there was potential public health harm, though spread of MDR HIV, if these patients were not effectively treated.
- 8.7 The Committee considered there had been significant advances in antiretroviral therapy over the 18 months since PHARMAC was approached by [redacted withheld under s9(2)(a) of the OIA]. The Committee considered that the issue was no longer one of recycling old drugs with partial activity but was rather the introduction of new treatments such as raltegravir and darunavir.
- 8.8 The Committee considered that with the introduction of new treatments the goal in MDR HIV patients was now achievement and maintenance of HIV viral load below detectable levels (<1.7 logs or <50 copies per mL).
- 8.9 The Committee noted that new treatments were now available including those for which funding applications had been received by PHARMAC; darunavir, a new protease inhibitor (PI) and raltegravir an inhibitor of HIV integrase strand transfer.
- 8.10 The Committee noted that in the pivotal darunavir studies, POWER 1 and 2 (Clotet et al, Lancet 2007, 369: 1169-78) in patients with extensive PI resistance, 58% of patients

treated with darunavir plus enfuvirtide (first time usage) achieved undetectable viral load by 48 weeks, compared with 44% on darunavir and 10% on placebo. Members noted that the response obtained at 24 weeks was sustained to 48 weeks in 92% of patients. Members concluded that the data demonstrated that in patients with MDR HIV the combination of darunavir with a second new class antiretroviral, such as enfuvirtide, had substantial and sustained efficacy when added to OBT.

- 8.11 The Committee noted that data from the raltegravir studies BENCHMRK 1 and 2 (Steigbigel et al. Abstract 571b. 16th Conference on Retroviruses and Opportunistic Infections Montreal 2009) demonstrated that 74% of patients treated with raltegravir plus enfuvirtide and 71% on raltegravir plus darunavir achieved undetectable viral load by 96 weeks. Members noted that the responses seen at 24 weeks (82% and 68% respectively) were therefore maintained through to 96 weeks in most patients.
- 8.12 The Committee reviewed a cost utility analysis from PHARMAC staff. The Committee noted that, due to the lack of clinical trials on the combined treatment regimen, the analysis was based on the POWER trial but assumed that the increase in viral load from week 20 was reduced by half with the combined treatment regimen (reflecting both the increased effectiveness and different patient population) resulting in a time until virological failure of 25 months. The Committee noted that this was nearly double the time until virological failure observed with a single agent, however the Committee considered that viral suppression is likely to be maintained inevitably with the combined treatment regimen. The Committee **recommended** that PHARMAC staff amend the cost-utility analysis to assume higher levels of efficacy with treatment, and also to include subgroup (darunavir/raltegravir) 96 week data from the BENCHMRK studies. Members also considered that efficacy in a New Zealand population may be better than seen in the studies since these patients would be unlikely to have the amount of virological resistance at baseline compared with the study populations.

9 Erlotinib (Tarceva) for Non Small-Cell Lung Cancer

Application

- 9.1 The Committee reviewed a re-application from Roche Products for the listing of erlotinib on the Pharmaceutical Schedule for the second-line treatment of patients with locally-advanced or metastatic non-small cell lung cancer (NSCLC).

Recommendation

- 9.2 The Committee **recommended** that erlotinib be listed in the Pharmaceutical Schedule for the second-line treatment of patients with advanced or metastatic NSCLC. The Committee gave this recommendation a low priority.
- 9.3 The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support*

services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (vii) The direct cost to health service users.

Discussion

- 9.4 The Committee noted that it had previously considered an application for erlotinib in May 2006 and concluded that the cost was high relative to modest clinical benefit, and recommended the application be declined. Members noted that in this re-application, although no new clinical trials have been published, Roche provided further discussion on the evidence in support of erlotinib, further analysis of the pivotal phase III study, BR.21, data from a large phase IV, open label, non-randomised cohort study (TRUST), and data from an open label phase IIIb study that was stopped early due to FDA approval (Spigel et al Cancer. 2008 Jun 15;112(12):2749-55).
- 9.5 The Committee noted that the re-application had been reviewed by CaTSoP at its February 2009 meeting and noted its recommendations.
- 9.6 The Committee reiterated its view that there was an unmet clinical need in patients with advanced NSCLC, for whom the prognosis is poor, but considered that erlotinib provided only a modest benefit compared with best supportive care.
- 9.7 The Committee considered that although it seemed that some patients responded well to erlotinib, for example non-smokers, patients with EGFR mutations or patients who develop a skin rash on treatment, it would be difficult to target those patients prospectively.
- 9.8 The Committee noted that there were no studies directly comparing erlotinib with other second line treatments, in particular docetaxel. Members considered that indirect comparison of data from a representative docetaxel study (Shepherd et al J Clin Oncol 2000;18:2095-2103) showed that erlotinib was likely to have similar efficacy but may be better tolerated than docetaxel and was certainly more convenient for patients to take. However, members noted that comparisons were confounded since the populations studied were not directly comparable (in terms of performance status) and the docetaxel studies had been performed some years earlier.
- 9.9 The Committee noted that NICE in the UK considered that "erlotinib could not reasonably be considered to have an overall survival benefit when compared with docetaxel, and that a progression-free survival benefit with docetaxel was more probable" (NICE, Final Appraisal Determination – Erlotinib for the treatment of non-small cell lung cancer, September 2008, paragraph 4.11).
- 9.10 The Committee considered that if funded, erlotinib would increase the overall number of patients accessing treatment for advanced NSCLC, principally because these patients would not need to access constrained DHB infusion services, unlike docetaxel treatment. Members further considered that funding erlotinib in the second line setting would shift docetaxel to third-line use.
- 9.11 The Committee noted that Maori have worse outcome with NSCLC compared with NZ Europeans. Members considered this was likely due to under-servicing at earlier stages of disease (screening, diagnostic, radiotherapy and first-line chemotherapy treatment).

Members considered that funding erlotinib would not address the disparity and addressing under-servicing at earlier stages of disease should be a higher priority for investment by the health sector.

- 9.12 The Committee considered that the cost of erlotinib was high relative to its modest benefit. In particular members did not agree with the suppliers view that it would be cost saving compared with docetaxel, when taking into account the increased numbers of patients likely to access treatment and the price reduction on docetaxel expected shortly as a result of patent expiry.