

## PTAC meeting held 23 & 24 July 2008

### (minutes for web publishing)

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#### Guidelines 2002:

“**Minute**” means that part of the record of a PTAC or Sub-committee meeting (including meetings by teleconference and recommendations made by other means of communication) that contains a recommendation to accept or decline an application for a new investment or a clinical proposal to widen access and related discussion.”

Note that this document is not necessarily a complete record of the PTAC meeting; records relating to PTAC discussions about an application that do not contain a recommendation to accept or decline an application have not been published and some material has been withheld in accordance with the following withholding grounds in the Official Information Act 1982 (OIA) to:

- protect the privacy of natural persons (section 9(2)(a);
  - 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));
  - enable PHARMAC to carry on, without prejudice or disadvantage, negotiations, including commercial negotiations (section 9(2)(j)).
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## **1 Record of PTAC meeting held 8 & 9 May 2008**

- 1.1 The Committee reviewed the record of the PTAC meeting held on 8 & 9 May 2008 and made the following minor amendments:
  - 1.1.1 Antiretrovirals (nPEP) – paragraph 2.11: replace “patients who have had shared intravenous injecting” with “patients who have shared intravenous injecting”.
  - 1.1.2 Zolmitriptan (Zomig) – paragraph 5.8: replace “reduce the use of non-triptan antimigraine treatments significantly” with “reduce the use of non-triptan antimigraine treatments”.

## **2 Acetylcholinesterase inhibitors for the Treatment of Alzheimer’s disease (donepezil, galantamine, rivastigmine)**

- 2.1 The Committee noted that it had reviewed the funding status of the acetylcholinesterase inhibitors (AChEIs) donepezil, rivastigmine and galantamine at its meeting in February 2008 and that it had requested that PHARMAC staff perform a budget impact analysis (BIA) and present this to the Committee.
- 2.2 The Committee noted that the BIA assumed that access to AChEIs would be limited to use within specialist mental health for elderly or geriatric services, and considered that this was appropriate.
- 2.3 The Committee considered that the assumptions in the BIA were appropriate, although somewhat conservative, as the patient numbers did not include other types of dementia that would likely be treated with AChEIs and the analysis assumed a relatively short duration of treatment. Some members considered, however, that higher actual patient numbers may be offset to some extent by the presence of co-morbid conditions in what is an elderly source population, where the presence of cardiac and other contraindications would affect uptake. The Committee noted that there was a risk that patients admitted to rest homes would continue to receive chronic treatment, when it was unlikely that significant benefit would be received, because the disease had already progressed to the point that the patient had become institutionalised.
- 2.4 The Committee noted that the BIA estimated the year one cost to the Pharmaceutical Budget of funding AChEIs to be approximately \$16 million, rising to \$24 million and \$32 million in years two and three. The Committee noted that generic entry could reduce the costs by approximately 50%.
- 2.5 The Committee noted that previous PHARMAC analyses and recent international analyses indicate that the cost per quality-adjusted life year (QALY) gained from AChEI treatment is unlikely to be less than \$50,000. The Committee noted that PHARMAC staff

plan to undertake further assessment of AChEI treatments to establish their cost-effectiveness in the New Zealand setting with the availability of generics.

- 2.6 The Committee considered that the use of AChEIs would not reduce the use of any currently funded pharmaceuticals to a significant degree.
- 2.7 The Committee considered that the patient population most likely to benefit from AChEI treatment would be patients with mild-to-moderate dementia (Dementia of the Alzheimer's type and Lewy Body Dementia) living in the community (i.e. not in a rest home) with adequate social support. The Committee noted that the evidence supported a modest benefit, on average, from AChEI treatment in this patient group.
- 2.8 The Committee noted that one of the key difficulties with AChEIs was the inability to effectively target therapy to those most likely to benefit. The Committee considered that if AChEIs were to be funded, the following Special Authority restrictions should apply:

SAXXX Special Authority for Subsidy

Initial application from any relevant practitioner. Applications valid for six months for applications meeting the following criteria:

All of:

1. Applicant works in a DHB specialist health service for older people;
2. Patient has mild-to-moderate Dementia of the Alzheimer's type or Lewy Body Dementia; and
3. Patient is living in the community (not in institutional care) and has adequate social support.

Renewal from any relevant practitioner. Applications valid for six months for applications meeting the following criteria:

1. The treatment remains appropriate; and
2. The patient has demonstrated a significant and sustained benefit from treatment (applicants are encouraged to consider stopping therapy where the patient has been institutionalised, as this could indicate disease progression to the extent that the treatment could no longer be considered effective).

- 2.9 The Committee considered that the AChEIs were similar to the extent that it would be reasonable to choose to fund one over the others based on price. However, the Committee considered that if only one AChEI were to be funded where there were no appreciable differences in price, then a once-daily treatment would be preferred over a twice-daily treatment, because of the likelihood of improved compliance from once-daily treatments. Members considered that up to 20% of patients would not tolerate treatment with a first AChEI but a proportion of these patients may be able to tolerate treatment with a second AChEI, and in this respect it would be useful to fund more than one AChEI.
- 2.10 The Committee noted correspondence from [withheld under sections 9(2)(a) of the OIA ] regarding the positive effect AChEI treatment had had on his life. The Committee noted that such experiences were not uncommon in individual patients.
- 2.11 Based on the evidence provided, including evidence presented at its February 2008 meeting, the Committee **recommended** that acetylcholinesterase inhibitors be listed in the Pharmaceutical Schedule under the proposed Special Authority criteria with a low

priority. The Committee noted that this recommendation was essentially unchanged from its previous recommendation in 2003.

- 2.12 The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other 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;* (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 Vigabatrin (Sabril) for the Treatment of Infantile Spasms**

- 3.1 The Committee considered a request from a clinician to widen access to vigabatrin for the first-line treatment of infantile spasms. The Committee noted that the use of vigabatrin for the treatment of infantile spasms was discussed by the Committee in November 2000, but at the time this was not a registered indication. The Committee noted that vigabatrin was now registered for the treatment of infantile spasms.
- 3.2 The Committee considered that the quality of the evidence supplied by the clinician (a published review article) was poor; however, the Committee noted that further information had been supplied by PHARMAC staff and that Committee members had sourced additional publications.
- 3.3 The Committee noted that the prognosis for patients with infantile spasms is poor, with a high incidence of severe mental retardation and development of the Lennox-Gestaut syndrome of intractable epilepsy.
- 3.4 The Committee considered that there were several other currently funded treatments that could be used in the treatment of infantile spasms, including corticosteroids (in particular tetracosactrin) and high-dose sodium valproate (noting that infantile spasms is not a registered indication for sodium valproate). However, the Committee considered that the evidence supported a niche role for vigabatrin in the treatment of infantile spasms associated with tuberous sclerosis complex, with responses seen in up to 62% of patients.
- 3.5 The Committee noted that vigabatrin is associated with a high risk of visual field defects, which may be asymptomatic in the early stages. The Committee noted that vigabatrin is currently restricted under a Special Authority as second-line treatment for epilepsy with a requirement for visual field testing unless this is impractical or impossible due to co-morbid conditions. The Committee considered that clinical judgement is required to assess the risks and benefits of vigabatrin treatment in cases where children cannot be expected to cooperate with visual field testing.

- 3.6 The Committee considered that, if access to vigabatrin was widened to include first-line treatment of infantile spasms, the patient numbers would be very small (less than 20 per year) and the financial risk would be low.
- 3.7 The Committee **recommended** that access to vigabatrin be widened, under the existing Special Authority, to include first-line treatment of infantile spasms, with a high priority.
- 3.8 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.*

#### **4 Aprepitant (Emend) for control of nausea associated with emetogenic cancer chemotherapy**

- 4.1 The Committee noted that it had reviewed applications from Merck Sharp & Dohme and from Waikato DHB to fund aprepitant (Emend) for control of nausea associated with emetogenic cancer chemotherapy at its meeting in November 2007, and had recommended deferring the application pending review by the Cancer Treatments Subcommittee of PTAC (CaTSoP) and receipt of further information regarding the effect of aprepitant on hospital stays and re-admission rates.
- 4.2 The Committee noted the minute relating to aprepitant from CaTSoP's March 2008 meeting.
- 4.3 The Committee noted that neither applicant had been able to provide information relevant to New Zealand regarding the effect of aprepitant on hospital stays and re-admission rates. The Committee noted that CaTSoP considered it unlikely that aprepitant would reduce hospital stays.
- 4.4 The Committee reiterated its previous view that there was a need for improved control of nausea and vomiting in patients undergoing highly emetogenic chemotherapy.
- 4.5 The Committee noted that at current prices the incremental cost-utility ratio was relatively high compared with other pharmaceuticals currently being considered for funding.
- 4.6 The Committee considered that there may be additional gains from treatment with aprepitant in patients who may otherwise discontinue chemotherapy due to nausea and vomiting.
- 4.7 The Committee noted that CaTSoP had recommended including aprepitant in the discretionary community supply (DCS) list. The Committee noted that PHARMAC applies the same decision criteria to changes to the DCS list as to Section B of the Pharmaceutical Schedule.

- 4.8 The Committee considered that aprepitant was more suited to the DCS list than to a community Pharmaceutical Schedule listing, mainly because of the way aprepitant is packaged and dispensed.
- 4.9 The Committee **recommended** that aprepitant be included on the DCS list, with a medium priority, for the control of nausea and vomiting in patients undergoing highly emetogenic chemotherapy.
- 4.10 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.*

## **5 Pemetrexed for first-line treatment of locally advanced or metastatic non-small cell lung cancer where histology is either adenocarcinoma or large-cell carcinoma**

- 5.1 The Committee considered an application from Eli Lilly for the listing of pemetrexed disodium (Alimta) on the Pharmaceutical Schedule for the first-line treatment of non-small cell lung cancer (NSCLC) in patients with adenocarcinoma or large cell carcinoma (i.e. non-squamous).
- 5.2 The Committee noted that it had previously reviewed an application for the use of pemetrexed in the second-line treatment of locally advanced or metastatic NSCLC on three occasions, and had recommended that the application be declined on the basis that the evidence showed no additional efficacy benefit of pemetrexed compared with docetaxel, which is currently funded for second-line treatment of NSCLC.
- 5.3 The Committee noted that the supplier had proposed the following Special Authority criteria for first-line funding:

Applications only from a relevant specialist. Approvals valid for 12 months.

Prerequisites

1. Patient has Non-Small Cell Lung cancer; and
2. Stage IIIa or above disease; and
3. Histology is either Adenocarcinoma or Large cell carcinoma

- 5.4 The Committee reviewed evidence from a phase three study comparing pemetrexed/cisplatin (PC) with gemcitabine/cisplatin (GC) (study H3E-MC-JMDB). Members noted that this was a randomised, open label, non-inferiority study in chemotherapy naive patients with Stage IIIB (not amenable to curative treatment) or Stage IV NSCLC and good performance status (ECOG 0 or 1). Patients were randomised to receive either pemetrexed 500 mg/m<sup>2</sup> plus cisplatin 75 mg/m<sup>2</sup> day one

every 21 days (PC) or gemcitabine 1250 mg/m<sup>2</sup> days one and eight plus cisplatin 75 mg/m<sup>2</sup> days one every 21 days (GC). Members noted that patients were given dexamethasone, folic acid and B12 during treatment. Members noted that treatment was continued until progressive disease, unacceptable toxicity, the investigator decided to discontinue the patient, or the patient requested discontinuation.

- 5.5 The Committee noted that a total 862 patients were randomised to the PC arm and 863 patients were randomised to the GC arm, of which 1669 patients received study treatment consisting of at least one dose of pemetrexed, cisplatin, or gemcitabine (PC, n = 839; GC, n = 830). Members noted that the treatment groups were well matched for age, sex, smoking history, disease stage, histological subtype and ECOG performance status. The median number of cycles of treatment in both treatment arms was five (mean 4.3, range 1-8). Members noted that the primary endpoint was overall survival, with secondary endpoints being progression-free survival, time to progression, time to treatment failure etc.
- 5.6 The Committee considered that there was no difference between treatment groups in median overall survival time, which was 10.3 months for both treatment groups, with one- and two-year survival rates of 43.5% and 18.9%, respectively, for the PC arm and 41.9% and 14%, respectively, for the GC arm. Similarly there was no difference in progression-free survival time which was 4.8 months for patients in the PC arm and 5.1 months in the GC arm.
- 5.7 The Committee noted that patients in the GC arm experienced more haematological adverse events and alopecia than patients treated with PC, but that anorexia and nausea were more common in patients treated with PC than GC. Members also noted that there were no significant differences in hospital admissions or hospital days but that there were more transfusions in patients treated with GC.
- 5.8 The Committee noted that a pre-specified analysis of overall survival by histology was also performed. In this analysis overall survival was statistically significantly increased in patients treated with PC compared with GC in patients who had large cell (10.7 months vs. 6.7 months) or adenocarcinoma (12.6 months vs. 10.9 months), whereas squamous cell carcinoma patients did better with GC compared with PC (10.8 months vs 9.4 months) Neither treatment was superior in patients classified as "other" histology (those that did not qualify as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma).
- 5.9 The Committee noted that the supplier had also conducted retrospective, unplanned, analyses of outcome based on histology on other older studies that had compared pemetrexed with docetaxel in Stage IIB/IV NSCLC, including the JME1 trial (J Clin Oncol. 2004 May 1;22(9):1589-97 a phase three study, H3E-MC-JMEN). Members noted that results of these retrospective, unplanned, analyses are suggestive of an efficacy advantage for pemetrexed in patients with combined non squamous histology; however, the benefit was small at approximately 1.3 months.
- 5.10 The Committee considered that overall the strength and quality of evidence provided was limited, as it was based on only one phase three study and retrospective, unplanned, analyses of other studies. Members considered that the evidence provided did suggest an efficacy advantage for pemetrexed in patients with non-squamous cell carcinoma histology; however the benefit was small and the results should ideally be repeated in

another prospective randomised trial. Members considered that even in patients with non-squamous cell carcinoma, pemetrexed offered only a very small benefit and was more expensive than other treatment options including vinorelbine, paclitaxel and gemcitabine in combination with cisplatin.

- 5.11 The Committee **recommended** that pemetrexed be listed on the pharmaceutical schedule but only if cost neutral compared with other treatment options including vinorelbine, paclitaxel and gemcitabine.
- 5.12 The Decision Criteria Particularly Relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services,* and (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## **6 Exenatide (Byetta) for type two diabetes mellitus**

- 6.1 The Committee considered a re-application from Eli Lilly for the listing of exenatide (Byetta) on the Pharmaceutical Schedule for the treatment of patients with type 2 diabetes.
- 6.2 The Committee noted that it had considered an application from Eli Lilly for the listing of exenatide at its August 2007 meeting and had recommended that the application be declined. The Committee noted that the re-submission included longer term data (minimum of three years) of exenatide (10 µg BID); some additional information regarding patients' baseline HbA1c and predictive factors for glycaemic control and weight loss; and evidence of the use of exenatide in combination with thiazolidinediones (TZD). Members noted that the original three key studies were again provided (DeFronzo et al. 2005; Buse et al. 2004; Kendall et al. 2005).
- 6.3 The Committee noted that Eli Lilly had recently applied to Medsafe for an amendment to the exenatide datasheet to include the use of exenatide with a thiazolidinedione. Members noted that the proposed Special Authority now included use of exenatide in combination with a thiazolidinedione as follows:

INITIAL APPLICATION - Patients with Type 2 diabetes.

Applications only from a relevant specialist. Approvals valid for 1 year.

(Endocrinologists, Diabetologists and General Physicians only)

A. In addition to the combination of either a sulphonylurea and metformin or a TZD and Metformin.

For use in addition to the combination with sulphonylurea and metformin or a TZD and metformin for patients who after diet and lifestyle changes and a six-month trial of the maximum tolerated dosages have poor glycaemic control (defined as HbA1c > 7.5% measured within the last month of the six month period).

B. In Combination with Metformin

For use in combination with metformin for patients who after diet and lifestyle changes and a six-month trial metformin, titrated to maximum effective dosage, have poor glycaemic control (defined as HbA1c > 7.5% measured within the last month of the six month period).

And

Sulphonylurea is contraindicated or not tolerated, or the patient is obese.

C. In Combination with Sulphonylurea

For use in combination with a sulphonylurea for patients who after diet and lifestyle changes and a six-month trial of sulphonylurea, titrated to maximum effective dosage, have poor glycaemic control (defined as HbA1c > 7.5% measured within the last month of the six-month period).

And

Metformin is contraindicated or not tolerated after a minimum of a four-week trial period

D. In Combination with a TZD

For use in combination with A TZD for patients who after diet and lifestyle changes and a six month trial of the maximum tolerated TZD have poor glycaemic control (defined as HbA1c > 7.5% measured within the last month of the six month period).

And

Sulphonylurea is contraindicated or not tolerated, or the patient is obese.

And

Metformin is contraindicated or not tolerated after a minimum of a four-week trial period.

Not to be used in combination with Insulin

RENEWAL - Patients with type 2 diabetes

Applications only from a relevant specialist

Approvals valid for 1 year where the patient continues to derive benefit from treatment.

- 6.4 The Committee noted the open label extension trial by Klonoff et al. 2008 from the original double blind studies. The Committee noted that this study involved 217 patients who had completed three years treatment with 10 µg BID exenatide whereby a reduction in HbA1c of 1% was sustained from baseline, with little change from week 122 to week 156. The Committee noted that the results also showed that the target HbA1c of 7% was achieved by 46% of patients and that weight progressively decreased by 5.3 kg below baseline. However, although there was a requirement at screening for a stable weight prior to entering the study, this was defined as a variation up to +/- 10 kg, raising a question as to the significance of a five kg weight change in the trial, particularly as the average weight of patients approached 100 kg. Members noted that patients with elevated ALT showed a reduction in level over time, with normalisation in 41%. Members noted that the results showed improvements in blood pressure, lipid profiles and insulin sensitivity, as measured by HOMA-B. However, members noted that only about 15% of patients remained in the study at the end of the three years.
- 6.5 The Committee noted the evidence from a phase three study of the use of exenatide in combination with a thiazolidinedione in patients with type 2 diabetes who were sub-optimally controlled with a thiazolidinedione with or without metformin (Zinman et al 2007). The Committee noted that this study concluded that exenatide improved glycaemic control and reduced body weight but was associated with gastrointestinal side effects. Members noted that the withdrawal rate from this study due to adverse events was 16% for exenatide and 2% for placebo and that the withdrawals increased as the dose was increased from five µg twice daily to 10 µg twice daily.
- 6.6 The Committee noted its previous concerns about the number of patients enrolled in the originally provided studies that had HbA1c below 7.5%. Members noted that the supplier

had responded that only a small number of patients (<15%) from the three key studies had a baseline HbA1c in the range 7.1% to 7.5%.

- 6.7 The Committee also noted its previous concerns about the correlation between change in body weight and change in HbA1c and the high rate of nausea reported. The Committee noted that nausea is a major adverse effect occurring in up to 60% of patients, but generally waning with time and noted that only about 4% of patients withdrew as a result of nausea in the DeFronzo et al. study. The Committee noted that the supplier had responded to the statistically significant correlation between change in body weight and change in HbA1c in the three key studies and considered that the correlation was weak.
- 6.8 The Committee queried whether post-marketing surveillance data was available. The Committee also noted the abstract by Drucker et al 2008 that showed exenatide once weekly results in significantly greater improvements in glycaemic control compared with exenatide twice daily in patients with type 2 diabetes. Members considered this information should be provided for consideration.
- 6.9 The Committee considered the mode of action, and the beneficial effects on weight and lipid profile makes exenatide a potentially useful agent in treatment of type 2 diabetes. Members noted that once weekly administration may become a very attractive treatment option.
- 6.10 The Committee noted that comparative studies with insulin glargine and biphasic insulin aspart had previously been provided and insulin treatment remained cheaper than the proposed prices for exenatide. The Committee considered that exenatide had limited additional benefits and high cost.
- 6.11 The Committee **recommended** that the application to list exenatide on the Pharmaceutical Schedule be declined at this time. Members recommended that this minute be provided to the Diabetes Subcommittee for comment.
- 6.12 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## **7 Proposed New Zealand Rheumatoid Association Guidelines of Ankylosing Spondylitis Patients for anti-TNF therapy**

- 7.1 The Committee reviewed an application by the New Zealand Rheumatology Association (NZRA), which included proposed treatment guidelines for the use TNF inhibitors in the treatment of ankylosing spondylitis.

- 7.2 The Committee noted that it currently recommended listing of adalimumab or another TNF inhibitor on the Pharmaceutical Schedule with a low priority, and that it had requested that the NZRA be consulted over targeting criteria in November 2006.
- 7.3 The Committee considered that the proposed criteria appeared to be a less restrictive version of the Australian Pharmaceutical Benefits Scheme criteria, and that they would not act as a reasonable constraint, and thus were unlikely to improve the cost-effectiveness and budgetary impact. In particular, the committee noted that in the PBS criteria there is a requirement for a C-reactive protein (CRP) criterion to be satisfied. The committee also noted that the proposed criteria were presented without any referencing or other justification or explanation.
- 7.4 Members noted that some patients with ankylosing spondylitis are severely affected by inflammatory disease while the majority are able to manage satisfactorily with existing treatments. The Committee further noted that some patients achieve dramatic responses to treatment with an anti-TNF agent while others gain relatively little. The treatment challenge is, therefore, to identify those who are most likely to benefit while acknowledging the very high treatment cost. The lack of objective disease activity markers and indicators of response to treatment is seen as a problem in making effective treatment available to the appropriate patient group.
- 7.5 Members reviewed the results of papers by Boonen et al (Ann Rheum Dis. 2006 Feb;65(2):201-8.), Botteman et al (Rheumatology (Oxford). 2007 Aug;46(8):1320-8.), Wailoo et al (Rheumatology (Oxford). 2008 Feb;47(2):119-20.), van der Heijde et al (Arthritis Rheum. 2006 Jul;54(7):2136-46.) and Zochling et al (Ann Rheum Dis. 2006 Apr;65(4):423-32.) as well as clinical trial reports for adalimumab studies M03-606 and M03-607. The National Institute of Health and Clinical Excellence (NICE) appraisal was also considered (McCleod C et.al (Health Technology Assessment 2007, 11(28):1-174), in particular Appendix 5 pp 125-139, which considered cost-effectiveness of TNF-inhibitors in the United Kingdom (UK) in relation to continuation of treatment based on clinical responses.
- 7.6 In respect to using a CRP criterion to limit access to a TNF inhibitor for ankylosing spondylitis, the Committee noted that in the paper by van der Heijde et al, 61.2% of patients treated with infliximab were ASAS20 responders at 24 weeks, compared with 19.2% in the placebo arm. For ASAS40 response criteria, the response rates were 47% and 12% for infliximab and placebo respectively. Members noted that the median Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) improvement over 24 weeks was 2.9 points for infliximab and 0.4 points for placebo. Members also noted that in patients with CRP greater than three times the upper limit of normal, the ASAS response rate was 72% compared with 15% of placebo treated patients.
- 7.7 The Committee noted that in the adalimumab clinical trial report M03-607, patients with elevated CRP levels had significantly better response to adalimumab than other patients, as did patients with BASDAI scores at baseline of four to six, and six or greater. Similar results were obtained in the clinical trial report M03-606. Members noted that these subgroup analyses had not been published, but that the reports provided evidence to justify an inflammatory marker, and a baseline BASDAI score as criteria for access to treatment with a TNF inhibitor.

- 7.8 The Committee noted the results of the NICE appraisal on the cost-effectiveness of TNF-inhibitors in the UK. In particular, the Committee noted that the sensitivity analysis indicated that the cost-effectiveness improved substantially if a larger improvement in BASDAI scores was obtained. The Committee considered that this could be applied to Special Authority criteria.
- 7.9 The Committee noted the results of a published cost-utility analysis (Botteman et al, 2007), which indicated that TNF-inhibitors were reasonably cost-effective in the UK clinical setting. However, members noted that the results of this analysis were significantly different to other published analyses for ankylosing spondylitis, and that the primary reason for this difference was the presumed duration of response.
- 7.10 The Committee noted that estimates of the likely patient population varied significantly, but considered that the NZRA estimate of 80 patients was probably more accurate than other estimates.
- 7.11 The Committee recommended the following draft Special Authority criteria for the use of a TNF inhibitor for ankylosing spondylitis:

**Initial application** Any relevant practitioner.. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

- 1 Patient has a confirmed diagnosis of ankylosing spondylitis for more than six months; and
- 2 Patient has low back pain and stiffness that is relieved by exercise but not by rest; and
- 3 Patient has radiographically proven sacroiliitis grade 2 or more by New York criteria if symmetrical, or 3 or more if asymmetrical/unilateral; and
- 4 Patient has tried and not responded adequately to treatment with 2 or more non-steroidal anti-inflammatory drugs (NSAIDs), in combination with anti-ulcer therapy if indicated, while completing at least 3 months of an exercise regime supervised by a physiotherapist; and
- 5 Either:
  - 5.1 Patient has limitation of motion of the lumbar spine in the sagittal and the frontal planes as determined by a score of at least 2 on each of the lumbar flexion and lumbar side flexion measurements of the Bath Ankylosing Spondylitis Metrology Index (BASMI); or
  - 5.2 Patient has limitation of chest expansion by at least 2.5cm below the following average normal values corrected for age and gender, and

	18-24	25-34	35-44	45-54	55-64	65-74	75+
Sex	M:F	M:F	M:F	M:F	M:F	M:F	M:F
Mean (cm)	7.0:5.5	7.5:5.5	6.5:4.5	6.0:5.0	5.5:4.0	4.0:4.0	3.0:2.5

- 6 A Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of at least 6 on a 0-10 scale; and
- 7 Either:
  - 7.1 An elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour; or
  - 7.2 A C-reactive protein (CRP) level greater than 15 mg per litre

Notes:

The BASDAI must be determined at the completion of the 3 month exercise trial, but prior to ceasing NSAID treatment. The BASDAI must be no more than 1 month old at the time of initial application.

Both ESR and CRP measures must be no more than 1 month old.

**Renewal application** Any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

- 1 Following 12 weeks of treatment, BASDAI has improved by 4 or more points from baseline on a 10 point scale, or by 50%, whichever is less; and
- 2 BASMI has improved by at least one category over baseline; and
- 3 ESR or CRP is within the normal range; and
- 4 Physician considers that the patient has benefited significantly from treatment and that continued treatment is appropriate.

7.12 The Committee noted that the proposed criteria are significantly more restrictive than those proposed by the NZRA, and noted that the additional criteria would likely improve the cost-effectiveness of TNF inhibitors for this indication.

7.13 The Committee requested that PHARMAC staff update the cost-effectiveness and budgetary impact analyses on the basis of these draft recommended criteria, using data from clinical trial reports and published data as appropriate, and provide these to PTAC for the purposes of re-evaluating the priority rating.

## **8 Growth hormone for Prader-Willi syndrome**

8.1 The Committee considered the recommendations made by the PTAC Growth Hormone Subcommittee at its November 2007 and March 2008 meetings. These recommendations were:

8.1.1 That growth hormone treatment should be discontinued in patients whose BMI increased by 0.5 SDS or more in one year;

8.1.2 That patients undergo a DEXA scan prior to starting treatment and on an annual basis during treatment to better analyse the effects of growth hormone and therefore to provide evidence of its efficacy. In making this recommendation the Subcommittee noted that access to DEXA scans may be difficult for some patients living in remote areas;

8.1.3 That IGF-1 levels be monitored to ensure the dose of growth hormone is not too high and if IGF-1 levels are more than two standard deviations above the mean, the dose should be titrated down to bring IGF-1 levels closer to the normal range;

8.1.4 That if the age criterion (the child is over two years of age) was removed the following criterion be included:

- 8.1.5 Height velocity in patients under two years of age should be assessed over a minimum six month period from the age of 12 months, with at least three height or length measurements over this period demonstrating clear and consistent evidence of linear growth failure (height velocity < 25<sup>th</sup> centile).
- 8.2 The Committee noted that it had previously considered the minutes of the November Subcommittee meeting and had recommended that the proposed changes to the criteria be reviewed once the Subcommittee had given its view on the evidence for the treatment of patients under two years of age, and secondly, that any requirement for dual energy x-ray absorptiometry (DEXA) scanning should not be mandatory due to the difficulty in obtaining these scans in some areas.
- 8.3 The Committee noted that currently one criterion for access to growth hormone treatment is for patients to have a height below the 3<sup>rd</sup> centile. The Committee noted that this criterion was inserted as a surrogate for growth hormone deficiency, as growth hormone deficiency is difficult to measure in this group, and so that obese patients with a poorly managed diet would be excluded from access as rapid weight gain drives height velocity.
- 8.4 The Committee noted that the Subcommittee had recommended removing the criterion for patients having an initial height less than the 3<sup>rd</sup> centile, but that the criterion for a poor growth velocity should be retained.
- 8.5 The Committee noted the evidence for growth hormone treatment for patients under two years of age and considered that the data demonstrated reasonable evidence for growth improvement, and body composition improvement. The data did not demonstrate clear evidence for changes in motor development, cognitive function or head circumference.
- 8.6 The Committee noted that the Subcommittee was reluctant to use growth data for infants under one year of age as changes in nutrition have an effect on growth and that growth should be assessed on the basis of at least three height or length measurements over a period of no less than six months.
- 8.7 The Committee noted that removing the age criterion would give an effective minimum commencement age of 18 months. The Committee noted that the financial implication of this change to the age restriction is minimal.
- 8.8 The Committee noted that the Subcommittee's recommendations would allow more children with Prader-Willi Syndrome to be treated, in keeping with the original estimated patient numbers, at an estimated \$200,000 for ten extra patients.
- 8.9 The Committee noted that in the future there were likely to be issues related to the cessation of treatment once linear growth had ceased, as body composition, as opposed to linear growth, is the treatment goal being sought by the Prader-Willi Syndrome Association.
- 8.10 The Committee considered that the changes to the existing criteria as recommended by the Growth Hormone Subcommittee, were a reasonable balance between the need for objective evidence of efficacy and, as outlined by the Prader-Willi Syndrome Association, for the primary benefit of growth hormone treatment being improvement in body composition rather than height gain.

- 8.11 The Committee **recommended** that access to growth hormone be widened for patients with Prader-Willi Syndrome, in line with the Growth Hormone Subcommittee's recommendations, with a medium priority.
- 8.12 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.*

## **9 Treatment of Post-menopausal osteoporosis and Paget's disease with zoledronic acid**

- 9.1 The Committee considered an application from Novartis for the use of zoledronic acid infusion in the treatment of post-menopausal osteoporosis and of Paget's disease of bone.
- 9.2 The Committee noted that for osteoporosis, zoledronic acid was administered as a once-yearly 15-minute infusion. For Paget's disease it is given as a one-off dose, but another dose can be given after 12 months if the patient relapses. Members noted that, in contrast to most infusions, this could be administered in a general practice setting, but that not all General Practitioners would be resourced to administer it.
- 9.3 Members noted that key advantages of zoledronic acid infusion over oral bisphosphonates in the treatment of osteoporosis are the reduction in gastrointestinal side-effects, and the compliance advantage over oral bisphosphonates.
- 9.4 Members noted that in the primary care setting an additional fee may be associated with the consultation due to the additional time and consumables cost involved with administration of zoledronic acid infusion, which would be an additional cost to patients.

### **Paget's disease of bone**

- 9.5 The Committee noted a paper by Reid et al (N Engl J Med. 2005 Sep 1;353(9):898-908.), which presented the pooled results of two identical studies comparing the efficacy of zoledronic acid with risedronate over six months for the treatment of Paget's disease. Members noted that the studies used double-dummies and that patients were required to take calcium and vitamin D supplements.
- 9.6 Members noted that risedronate is not subsidised in New Zealand, and so is not the ideal comparator, although it is generally considered to be similar to alendronate in terms of its side effect profile and efficacy.
- 9.7 The Committee noted that the primary adverse effect from zoledronic acid infusion was the appearance of influenza-like symptoms, which seemed to resolve within a few days.

- 9.8 Members noted that zoledronic acid was significantly more effective than risedronate in normalising alkaline phosphatase (ALP) levels at six months. It was noted that serum ALP levels showed a more rapid and marked reduction in the zoledronic acid groups compared with the risedronate groups. The rates of therapeutic response reached 96% in the zoledronic acid group compared to 74% in the risedronate group at six months ( $p < 0.001$ ). The median time to a first therapeutic response was 64 days in the zoledronic acid group compared to 89 days in the risedronate group ( $p < 0.001$ ).
- 9.9 The Committee also noted the result of a follow-up extension in patient who responded to treatment at six months (J Bone Miner Res. 2007 Jan;22(1):142-8.). The Committee noted that at 24 months, 43% of the patients in the risedronate group had lost the therapeutic effect, as compared to 2% of the patients in the zoledronic acid group.
- 9.10 The Committee recommended that zoledronic acid be listed in the Pharmaceutical Schedule for the treatment of Paget's disease of bone, and gave a high priority to this recommendation.

### **Post-menopausal osteoporosis**

- 9.11 The Committee considered a paper by Black et al (N Engl J Med. 2007 May 3;356(18):1809-22.), a placebo-controlled study of zoledronic acid in 7765 post-menopausal osteoporotic women over three years.
- 9.12 Members noted that the paper indicated that zoledronic acid was effective in reducing the rate of vertebral fractures in previously untreated patients (3.3% vs. 10.9%) and in reducing the rate of hip fractures in all patients (1.4% vs. 2.5%).
- 9.13 Members noted that, infusions of zoledronic acid were generally well-tolerated, although post-dose effects such as pyrexia, myalgia and influenza-like symptoms were common. Members also noted that zoledronic acid was associated with an increase in serum creatinine levels, and a small increased risk of atrial fibrillation.
- 9.14 The Committee noted a paper by McClung et al (Bone. 2007 Jul;41(1):122-8.) that compared zoledronic acid infusions ( $n = 113$ ) with alendronate 70 mg ( $n = 112$ ) in patients that had previously been treated with weekly alendronate. Members noted that there were small gains in both treatment arms for lumbar spine bone mineral density (BMD), but that there was no significant difference between the treatment arms.
- 9.15 The Committee considered a paper by Lyles et al (N Engl J Med. 2007;357:nihpa40967) that reported the results of a study comparing zoledronic acid infusions ( $n = 1065$ ) with placebo ( $n = 1062$ ) in patients following surgical repair of a hip fracture. Members noted that zoledronic acid was associated with a reduction in clinical vertebral fractures (1.7% vs. 3.8%), non-vertebral fractures (7.6% vs. 10.7%) and an increase in BMD.
- 9.16 Members also noted that zoledronic acid was associated with a statistically significant reduction in mortality across the study (9.6% vs. 13.3%), and that there was no statistical difference in atrial fibrillation, and no evidence of osteonecrosis.
- 9.17 The Committee noted that zoledronic acid appears to have a more rapid and sustained improvement in BMD than oral bisphosphonates, and that its efficacy in treating post-menopausal osteoporosis is similar to alendronate.

- 9.18 The Committee noted that compliance with alendronate in clinical practice is often poor, mainly due to the gastrointestinal side-effects associated with treatment. The Committee therefore considered that zoledronic acid is likely to improve compliance with treatment in clinical practice.
- 9.19 The Committee **recommended** that zoledronic acid be listed in the Pharmaceutical Schedule for the treatment of post-menopausal osteoporosis in patients intolerant of oral bisphosphonates, and gave this recommendation a medium-high priority.
- 9.20 The Committee noted that the availability of zoledronic acid for second-line treatment of post-menopausal osteoporosis would likely reduce the need for the funding of raloxifene.
- 9.21 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; (vii) The direct cost to health service users.*

## **10 Adalimumab (Humira) for severe chronic plaque psoriasis**

- 10.1 The Committee considered an application from Abbott Australasia to list adalimumab (Humira) on the Pharmaceutical Schedule for the treatment of patients with severe chronic plaque psoriasis.
- 10.2 The Committee noted that the application proposed that adalimumab would be listed on the Pharmaceutical Schedule subject to a Special Authority whereby treatment is restricted to patients who have failed to demonstrate an adequate response, as demonstrated by a Psoriasis Area and Severity Index (PASI) assessment, to three of the following four treatments, where failure to achieve an adequate response is demonstrated by a PASI score of greater than 15:
- (i) phototherapy (UVB or PUVA) for three treatments per week for at least six weeks; and/or
  - (ii) methotrexate at a dose of at least 10 mg weekly for at least six weeks; and/or
  - (iii) cyclosporin at a dose of at least 2 mg per kg per day for at least six weeks; and/or
  - (iv) acitretin at a dose of at least 0.4 mg per kg per day for at least six weeks.

The Committee noted that the renewal criteria would be restricted to patients who demonstrated an adequate response as evidenced by a reduction in their PASI score of 75% or more.

- 10.3 The Committee noted the key evidence of efficacy provided in the form of two phase three randomised controlled trials (RCTs) and one phase two trial. Members noted that the principal clinical response measure used in the key trials was the proportion of patients achieving a PASI 75 response (i.e. at least a 75% reduction in PASI score relative to baseline). The Committee considered that the strength and quality of the evidence was moderate.

- 10.4 The Committee noted that the results of the two phase three RCTs (REVEAL and CHAMPION) showed that a statistically significantly greater proportion of people treated with adalimumab experienced a 75% or greater reduction in PASI score at 16 weeks compared with those who received placebo. Members noted that the REVEAL trial showed that this benefit was maintained over a period of 52 weeks, and continued to favour adalimumab over placebo.
- 10.5 The Committee noted that in the CHAMPION trial, patients administered adalimumab received a loading dose of 80 mg subcutaneously at week zero, followed by a dose of 40 mg every other week. The Committee noted that patients receiving methotrexate did not receive a loading dose, but rather the dose of methotrexate was increased slowly over time as required and tolerated. The Committee considered that this dosing schedule would have favoured adalimumab.
- 10.6 The Committee noted that no new safety issues were identified in the clinical trials; however, the Committee noted its previous comments regarding the safety issues in general with TNF inhibitors that have been made when considering other indications.
- 10.7 The Committee noted that the proposed Special Authority was for 16 weeks treatment of severe chronic plaque psoriasis. The Committee noted the trials provided included moderate chronic plaque psoriasis patients and showed that a PASI response of 75% is maintained between weeks 12 and 16. Members considered that the assessment of response to treatment could therefore occur after 12 weeks.
- 10.8 The Committee noted that in the REVEAL trial approximately two-thirds of patients who had an initial response to adalimumab maintained their response rate for 20 weeks after stopping adalimumab. The Committee considered that, in responders, a smaller maintenance dose or larger dosing intervals such as three or four weeks might be adequate to prevent relapse.
- 10.9 The Committee noted that the clinical trials showed that about 30% of patients did not have an adequate response; however, in clinical practice these patients may continue to be prescribed treatment even if there is only a relatively modest response and therefore patient numbers may be higher than proposed by the supplier.
- 10.10 The Committee considered that the proposed Special Authority criteria should be considered in more detail, possibly by a Dermatologicals Subcommittee or by obtaining individual expert advice from dermatologists who are using adalimumab. Members considered that targeting access would be difficult and that there was a risk that patients with less severe psoriasis may access treatment. The Committee also considered that there was a risk that patients may continue to receive treatment even if they had an inadequate response, and that these patients may have their dose increased to weekly dosing. The Committee therefore considered that the funding of adalimumab for severe psoriasis posed a very high fiscal risk. The Committee considered that the patient numbers included in the application were underestimated, and that PHARMAC should seek the advice of Dermatologists regarding likely patient numbers.
- 10.11 The Committee noted the cost-utility analysis provided by the supplier where the target population included patients with severe chronic plaque psoriasis who had failed systemic therapies. The Committee noted that PHARMAC staff had amended several inputs in the analysis (including the utility values and costs) and that these amendments

had increased the cost per quality-adjusted life year (QALY) of adalimumab. The Committee considered these amendments were appropriate. Members noted that the results of the analysis were sensitive to the assumed incremental utility of patients responding to treatment compared with non-responders. The Committee noted that the analysis did not include the severe adverse events associated with adalimumab, which are likely to further increase the cost per QALY.

- 10.12 The Committee noted that other biological agents (infliximab, etanercept, efalizumab, alefacept) were also registered for the treatment of psoriasis; however, there are no head to head studies showing superiority of any one agent.
- 10.13 The Committee considered that there was an unmet clinical need for severe chronic plaque psoriasis patients who had failed systemic treatments and that adalimumab was an effective treatment for these patients. The Committee **recommended** that adalimumab be listed on the Pharmaceutical Schedule with a medium priority. The Committee noted that other biological agents, as above, would be acceptable treatments and that a psoriasis panel with a capped budget could be established to contain expenditure. The Committee recommended that PHARMAC seek the advice from relevant specialists to ensure appropriate targeting criteria are used.
- 10.14 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## **11 Adalimumab (Humira) for the treatment of Crohn's disease**

- 11.1 The Committee considered an application from Abbott Australasia to widen access to adalimumab (Humira), as listed on the Pharmaceutical Schedule to include the treatment of Crohn's disease.
- 11.2 The Committee noted that it had considered an application from Abbott to widen access to adalimumab in August 2007; however, had deferred making a recommendation pending advice (including targeting criteria) from an ad-hoc Gastrointestinal Subcommittee. The Committee noted the advice and proposed Special Authority devised by the Gastrointestinal Subcommittee.
- 11.3 The Committee noted that a Cochrane review, which had been published since its last review, concluded that adalimumab had a similar effect as infliximab; however the Committee considered that there was no new evidence since the original application was considered.
- 11.4 The Committee noted that the Gastrointestinal Subcommittee had recommended wider access criteria than proposed by the supplier. The Committee considered that the Gastrointestinal Subcommittee proposed criteria were too broad. The Committee

considered that the criteria recommended by the National Institute of Health and Clinical Excellence (NICE) for the use of infliximab in Crohn's disease were more appropriate. These criteria restricted access to patients with severe active Crohn's disease (defined as having a score on the Crohn's Disease Activity Index (CDAI) of 300 or more) where treatment with immunomodulators and corticosteroids have not worked or have caused intolerable side effects, and where surgery is not an option. The renewal criterion was, in essence, patients who responded to the initial treatment but whose condition then got worse.

- 11.5 The Committee noted that the CLASSIC I trial had assessed the efficacy of adalimumab induction treatment at a dose of 80 mg on day 1, and 40 mg on day 14. The Committee noted that at week four, significantly more patients receiving high-dose adalimumab were in clinical remission compared with placebo, however there was no significant difference between remission rates of high-dose compared with low-dose induction. Members therefore considered that the high-dose induction regimen was not necessarily better than the lower dose regimen; however, it was noted that this lower dosing regime conflicted with the Medsafe datasheet. The Committee also noted that there was a high placebo response in the clinical trials.
- 11.6 The Committee noted the cost-utility analysis provided by PHARMAC staff that had been updated following the advice received from the Gastrointestinal Subcommittee. Members considered that the inputs and assumptions included in the cost-utility analysis were reasonable and noted that the estimated cost per quality-adjusted life year (QALY) of adalimumab for the treatment of Crohn's disease remained high.
- 11.7 The Committee considered that the patient population would likely be underestimated as a result of responders remaining on treatment for longer than necessary and patients with less severe Crohn's disease accessing adalimumab. The Committee also considered that patients not responding to treatment may receive weekly treatment, hence increasing the cost of adalimumab.
- 11.8 The Committee **recommended** that access to adalimumab be widened in the Pharmaceutical Schedule to include the treatment of Crohn's disease under the criteria proposed above and assigned a medium-high priority to this recommendation. The Committee noted that any TNF inhibitor indicated for Crohn's disease would be an acceptable treatment and also considered whether funding could be best provided through Discretionary Community Supply pharmaceuticals (part IV of Section H of the Pharmaceutical Schedule).
- 11.9 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule; (vii) The direct cost to health service.*

## 12 Calcipotriol and betamethasone dipropionate (Daivobet) for treatment of psoriasis

- 12.1 The Committee considered an application from CSL Biotherapies Limited to list betamethasone dipropionate 643µg/g (equivalent to 500 µg/g betamethasone) and calcipotriol 50µg/g (as calcipotriol hydrate 52.2µg/g) ointment (Daivobet) on the Pharmaceutical Schedule for the treatment of patients with psoriasis.
- 12.2 The Committee noted that Daivobet is a combination once-daily topical treatment containing betamethasone and calcipotriol and that both individual components are currently fully subsidised on the Pharmaceutical Schedule.
- 12.3 The Committee noted the key evidence of efficacy provided in the form of six short-term published studies (Kragballe and van de Kerkhof; Anstey and Kragballe; Salmhofer et al; Guenther et al; van de Kerkhof; van de Kerkhof et al). Members noted that the principal clinical response measure used in the key trials was the proportion of patients achieving a PASI 50 or PASI 75 response (i.e. at least a 50% or 75% reduction in PASI score relative to baseline).
- 12.4 The Committee considered that the studies confirmed the clinical efficacy of Daivobet and that it is significantly more effective than each of the individual components when used alone. Members noted that no studies were presented which compared Daivobet use with the individual components (calcipotriol and betamethasone) used in combination. The Committee noted that the supplier had claimed that, due to conflicting stability requirements, calcipotriol and betamethasone cannot be mixed or applied simultaneously. However, Members consider that there was no apparent reason why there should be any issue with applying the individual agents at different times.
- 12.5 The Committee considered that the safety profile of Daivobet was good and Daivobet would likely improve compliance amongst patients. However, the Committee considered that there could be a small risk from patients applying Daivobet twice daily and in larger amounts and, therefore, exposing themselves to more of the potent betamethasone steroid than they would have done otherwise.
- 12.6 The Committee noted the rapid cost-utility analysis provided by PHARMAC staff on Daivobet and agreed with the assumptions used in the analysis. Members noted that the individual components (calcipotriol and betamethasone) were significantly cheaper than the proposed price of Daivobet and that generic calcipotriol was expected in the short-term.
- 12.7 The Committee **recommended** that Daivobet be listed on the Pharmaceutical Schedule only if it was cost-neutral compared to the individual components of calcipotriol and betamethasone dipropionate.
- 12.8 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*

### **13 Blood ketone test strips (Optium Blood Ketone Test Strips)**

- 13.1 The Committee considered an application from Medica Pacifica for the listing of  $\beta$ -hydroxybutyrate test strips (Optium blood ketone test strips) on the Pharmaceutical Schedule for patients with type 1 diabetes.
- 13.2 The Committee noted that it had considered an application from Diabetes Youth NZ for blood ketone test strips to be listed on the Pharmaceutical Schedule in November 2007. The Committee noted that it had recommended that PHARMAC seek an application from a pharmaceutical supplier and that the Diabetes Subcommittee consider the application in the first instance. Members noted that the Diabetes Subcommittee had considered this application at its June 2008 meeting.
- 13.3 The Committee noted that the supplier proposed the following endorsement restriction be applied to blood ketone test strips:
- Either:
- Patient is a type 1 diabetic using an insulin pump. Maximum quantity of 12 packs per annum. No further prescriptions will be subsidised; or
- Patient is a type 1 diabetic using insulin by injection. Maximum quantity of 2 packs per annum. No further prescriptions will be subsidised.
- 13.4 The Committee noted that the key evidence provided was in the form of an open-label randomised study directly pertaining to the use of blood ketone testing by patients with type 1 diabetes (Laffel et al 2005). The Committee noted that this had been considered previously with the Diabetes Youth NZ application. The Committee noted four other short-term studies (Vanelli et al (2003); Taboulet et al (2004); Harris (2004) et al; Guerci et al (2003)) and a conference abstract (Fineberg et al (2000)) provided with the application. Members considered that the strength of evidence provided in the application was moderate; however, the quality of the trials were poor.
- 13.5 The Committee considered that blood ketone test has superior properties compared to urine ketone tests and provided more rapid results. The Committee noted that, if funded, blood ketone test strips would provide a benefit to patients with type 1 diabetes because of earlier detection of ketoacidosis.
- 13.6 The Committee noted the data from the Laffel et al study on the incidence of emergency department visits and hospitalisations that showed a lower reporting for patients testing with blood ketone test strips versus those testing with urine ketone test strips (38 per 100 patient years versus 75 per 100 years respectively). The Committee noted that Laffel et al. study reported that blood ketone testing resulted in 37 fewer acute complications requiring hospital visits or hospitalisation per 100 patients per year. Members felt that the number of hospitalisation with diabetic ketoacidosis may be lower in NZ compared to the trial data because of the good access to primary care and diabetic nurse educators. However, the Committee considered that blood ketone test strips, if funded, may reduce hospital admissions and patients presenting to emergency departments with

ketoacidosis, however the extent of this reduction in hospitalisations is uncertain and may be minimal.

- 13.7 The Committee considered that the patients with type 1 diabetes who would benefit the most from the funding of blood ketone test strips were those using insulin pumps and those prone to ketoacidosis who frequently present to hospital. The Committee considered that the proposed restrictions by the supplier were too wide and recommended the restriction be limited, as suggested by the Diabetes Subcommittee as follows due to the potential high fiscal risk:

Patient has type 1 diabetes and has had one or more episodes of ketoacidosis (excluding first presentation). Maximum quantity of 2 packs per annum. No further prescriptions will be subsidised.

- 13.8 The Committee noted a letter from Diabetes Youth New Zealand to PHARMAC that noted subsidising blood ketone test strips as their highest priority.

- 13.9 The Committee **recommended** that Optium blood ketone test strips be listed on the Pharmaceutical Schedule with a medium priority.

- 13.10 The Committee considered that it would be acceptable to apply reference pricing between brands of blood glucose test strips [ withheld under section 9(2)(j) of the OIA .]

- 13.11 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;* and (vii) *The direct cost to health service users.*

## 14 Insulin aspart (NovoMix 30) for the treatment of diabetes mellitus

- 14.1 The Committee reviewed an application from Novo Nordisk for the listing of 30% insulin aspart and 70% insulin aspart protamine suspension (NovoMix 30) on the Pharmaceutical Schedule for the treatment of diabetes mellitus. The Committee noted that the application had been considered in the first instance by the Diabetes Subcommittee at its June 2008 meeting.

- 14.2 The Committee noted that there were nine trials provided that compared NovoMix 30 with human insulin 30/70, of which only one provided long-term data (Trial 1353 – 48 weeks). The Committee considered that the strength and quality of the evidence was moderate.

- 14.3 The Committee noted that four of the trials were randomised double blind studies (Trial 1234, Trial 1466, Trial 3002, and Trial 3006) and four trials included patients with type 1 diabetes although the majority of patients had type 2 diabetes.

14.4 The Committee considered that a meta-analysis of the studies suggested that NovoMix 30, when compared with human insulin 30/70:

- lowered postprandial glucose increments after breakfast and dinner;
- was associated with higher fasting plasma glucose levels;
- did not affect HbA1c levels;
- did not affect the occurrence of minor hypoglycaemic episodes; and
- reduced the rate of major and nocturnal hypoglycaemic episodes.

However, the Committee noted that the event rates for hypoglycaemia, in particular for nocturnal and major hypoglycaemia, were low.

14.5 The Committee considered that, if listed, NovoMix 30 would be used preferentially over human insulin 30/70 (Humulin 30/70 and PenMix 30) and that a number of patients may switch from these products to NovoMix 30. Members also considered that short-acting insulin prescriptions may be reduced.

14.6 The Committee considered that NovoMix 30 would be used mainly in type 2 diabetes, as a large number of patients use twice-daily regimes of short- or rapid-acting insulin and intermediate-acting insulin, either as fixed combinations or separate injections. The Committee considered that in clinical practice NovoMix 30 would also be used in type 2 diabetes for patients initiating on insulin treatment.

14.7 The Committee noted that a significant number of type 1 diabetes patients were on twice daily mixtures, either premixed or as separate injections and some of these patients would also be moved to NovoMix 30. The Subcommittee considered that NovoMix 30 would increase compliance and therefore also be used in patients on intensive insulin regimes in place of separate morning injections of short- or rapid-acting insulin and intermediate-acting insulin.

14.8 The Committee considered that NovoMix 30 has the same or similar therapeutic effect as Humulin 30/70 and Penmix 30 and that the dose equivalency was approximately the same. Members noted that they had not seen comparative data between NovoMix 30 and Humalog Mix 25 (another biphasic analogue mix preparation containing 25% insulin lispro and 75% insulin lispro protamine suspension); however, members considered that, based on the data that they had evaluated comparing the two insulin preparations with human insulin 30/70, their therapeutic effects were the same or similar.

14.9 The Committee considered that, if NovoMix 30 was listed on the Pharmaceutical Schedule, reference pricing could occur between Humulin 30/70, Penmix 30 and Humalog Mix 25 (if listed). The Committee considered that it was not appropriate to run a sole supply process between Humulin 30/70, Penmix 30 and Humalog Mix 25 (if listed); however considered that it could be appropriate to run a sole supply process between NovoMix 30 and Humalog Mix 25. Members noted that Novo Nordisk and Eli Lilly used different delivery devices that had different advantages and convenience factors.

- 14.10 The Committee considered that patients who would benefit the most from NovoMix 30 were those treated unsuccessfully with oral agents and those using twice-daily insulin regimes who have inadequate glycaemic control. Members considered that, if listed, NovoMix 30 should not have any clinical restrictions applied.
- 14.11 The Committee **recommended** that 30% insulin aspart and 70% insulin aspart protamine suspension be listed on the Pharmaceutical Schedule only if it was cost-neutral compared to Humulin 30/70 and Penmix 30.
- 14.12 The Decision Criteria particularly relevant to this recommendation are: *(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; and (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.*

## **15 Latanoprost and timolol maleate (Xalacom) eye drops for glaucoma**

- 15.1 The Committee reviewed an application from Pfizer for the listing of latanoprost and timolol maleate (Xalacom) eye drops on the Pharmaceutical Schedule for the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension.
- 15.2 The Committee noted that it had considered latanoprost and timolol maleate eye drops in May 2005 and that it considered the combination product (combination therapy) to be slightly inferior to the individual components administered concomitantly (dual therapy), and recommended that the combination product should only be listed if cost neutral.
- 15.3 The Committee noted that the current application focused on two trials, a trial by Diestelhorst et al (2004) and a trial by Diestelhorst et al (2006). The Committee noted that it had reviewed the trial by Diestelhorst et al (2004) when it considered the 2005 application.
- 15.4 The Committee noted that the study by Diestelhorst et al (2004) compared combination and dual therapy in 190 patients in a 12-week, double masked, randomised, cross-over study. The Committee noted that in the combination group latanoprost was applied in the morning but in the dual group latanoprost was applied in the evening. The Committee noted that the study found a mean diurnal IOP of 17.0 mmHg after dual therapy and 15.9 mmHg after combination therapy ( $p < 0.0001$ ), and that the difference in mean within-patient diurnal IOP was 1.1 mmHg favouring dual therapy (95% CI 0.8 to 1.4 mmHg). The Committee noted that the trial did not meet the endpoint that combination therapy was not inferior to dual therapy.
- 15.5 The Committee noted that the study by Diestelhorst et al (2006) also compared combination and dual therapy in 502 patients in a 12-week, double masked, randomised,

cross-over study. The Committee noted that, in contrast to the 2004 study, latanoprost was applied in the evening in both the combination and dual therapy groups. The Committee noted that the difference in mean within-patient diurnal IOP was 0.3 mmHg favouring dual therapy but this was not statistically significant (95% CI -0.1 to 0.7 mmHg; p=0.15).

- 15.6 The Committee noted that the 2004 trial used a mean difference in IOP of less than 1.0 mmHg when determining whether combination therapy was inferior to the dual therapy but that in the 2006 trial this had increased to less than 1.5 mmHg even though the number of patients in the 2006 trial was significantly larger.
- 15.7 The Committee noted that the supplier suggested that the difference in the trial results could be accounted for by the timing of latanoprost dosing, with evening dosing being more effective at reducing the peak IOP. The Committee noted, however, that the datasheet does not indicate that evening dosing is preferred.
- 15.8 The Committee considered that the additional evidence supplied did not change its opinion that combination solution is slightly inferior to the individual components administered concomitantly.
- 15.9 The Committee noted that the supplier suggested that the combination product would result in increased compliance; however, the Committee noted that there was no evidence supplied to support this in patients with increased IOP, except for physician and patient opinion.
- 15.10 The Committee considered that the patients most likely to use the combination product would be those whose IOP was not adequately controlled on either of the components taken individually. The Committee also considered that patients well controlled on the individual components administered concomitantly would be unlikely to switch to the combination product.
- 15.11 The Committee reiterated its 2005 **recommendation** that latanoprost and timolol maleate eye drops only be listed on the Pharmaceutical Schedule if cost-neutral. The Committee also considered that in determining cost-neutral status, the availability of generic latanoprost should be taken into account.

## **16 Ranibizumab (Lucentis) for the treatment of neo-vascular (wet) aged-related macular degeneration**

- 16.1 The Committee noted a paper regarding the use of ranibizumab (Lucentis) for the treatment of wet age-related macular degeneration (AMD).
- 16.2 Members noted that the administration of ranibizumab is specialised, requiring an intraocular injection, and as such would either be administered by ophthalmologists in District Health Board (DHB) hospitals, or in private eye clinics. The Committee considered that because of this, a listing in the community section of the Pharmaceutical Schedule was not appropriate.

- 16.3 The Committee noted that most, but not all, DHBs were providing access to anti-VEGF (vascular endothelial growth factor) treatments, and that bevacizumab was commonly used off-label within DHBs. Members noted that some observational studies have indicated that ranibizumab and bevacizumab have similar efficacy. Members noted that bevacizumab was significantly less expensive, and therefore more cost-effective, than ranibizumab.
- 16.4 The Committee noted that the cost-effectiveness and budgetary impact of ranibizumab would depend on a number of assumptions that are subject to uncertainty including the optimal dosing schedule and duration of treatment, the assumed benefits of treatment and the disease progression with standard care (placebo or bevacizumab in New Zealand). Members noted that the cost-effectiveness of ranibizumab compared with standard care was therefore difficult to determine, but likely to be high and uncertain.
- 16.5 The Committee noted that two head-to-head trials comparing ranibizumab and bevacizumab are in progress. Results from these trials will be useful for DHBs to determine the most cost-effective product in treatment of AMD.
- 16.6 The Committee acknowledged that VEGF inhibitors could be associated with increased cardiovascular events due to their effect on new blood vessel formation. Combined analyses of ranibizumab trials have shown slightly increased risk of extra retinal bleeding and vascular events. Increased cardiovascular risks also have been demonstrated with bevacizumab.
- 16.7 The Committee upheld its previous **recommendation** to decline the application to list ranibizumab on the Pharmaceutical Schedule, and recommended a copy of the minute for its discussion be sent to the Ophthalmology Subcommittee.

## **17 Potassium citrate for recurrent calcium oxalate urolithiasis**

- 17.1 The Committee considered an application from a clinician regarding the use of potassium citrate in the treatment of recurrent calcium oxalate urolithiasis. Members noted that calcium oxalate is responsible for around 50% of renal calculi.
- 17.2 The Committee noted that the use of citrate salts is effective in reducing uric acid stones, but that sodium citrate, which is currently subsidised, may be associated with an increase in calcium oxalate stones. Members also noted that potassium citrate can be associated with epigastric pain, abdominal distention and diarrhoea.
- 17.3 The Committee noted a study of five patients with uric acid stones complicated by calcium stones (Kidney Int. 1983 Sep;24(3):348-52.), which compared potassium citrate with sodium citrate and indicated that, whereas both salts were effective for uric acid stones, only potassium citrate may assist in preventing the formation of calcium oxalate stones.
- 17.4 The Committee considered that sodium citrate was unlikely to be the best treatment for preventing renal calculi, but that there was no evidence to indicate that potassium citrate was the best treatment. Members noted that potassium-magnesium citrate is another alternative, although no comparative evidence was available. Members noted that there

had been very few applications under Exceptional Circumstances, and were unsure what other treatments were being used when sodium citrate was inappropriate.

- 17.5 The Committee noted the need for this product and **recommended** that it be listed on the Pharmaceutical Schedule with a high priority, and that PHARMAC staff should look to find a preparation. .
- 17.6 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; (vii) The direct cost to health service users (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.*

## 18 Oxybutynin patches (Oxytrol) for urinary incontinence

- 18.1 The Committee noted an application from Hospira for the use of oxybutynin patches in the treatment of urinary incontinence.
- 18.2 The Committee noted the results of some New Zealand population surveys, which indicated that of cases of urinary incontinence, half is stress incontinence, a quarter is urge incontinence and the remainder is mixed incontinence. Members note that urinary incontinence may be more prevalent in Maori, and that a majority of residents of residential care facilities is affected, and that relatively few patients are treated with short-acting oral oxybutynin due to side-effects.
- 18.3 Members noted that alternative treatments include biofeedback, pelvic floor exercises, anticholinergic agents, botulinum A toxin and bladder training.
- 18.4 The Committee noted the data provided in a review by Christian Hampel (Long-Term Management of Overactive Bladder with Antimuscarinic Agents. European Urology Supplements 6,(5):432-437), which indicated that persistence rates after 12 months' open-label use were 46% for oxybutynin extended release, 71% for tolterodine and 81% for solifenacin. Members noted that this review also indicated that persistence appeared to be higher for once-daily preparations than those that required multiple doses per day.
- 18.5 The Committee noted that the application did not mention the risk of confusion or falls, which are particularly important factors when using antimuscarinic therapy in elderly patients. Members noted that there is a preference to avoid the use of oxybutynin in elderly patients because of these adverse effects.
- 18.6 Members noted that most of the antimuscuranic agents have similar efficacy and recent advances in this field has been to improve tolerability of preparations.
- 18.7 Members considered that the efficacy of short-acting oral oxybutynin and transdermal oxybutynin appeared to be similar, although the side-effects differed between the two presentations.

- 18.8 The Committee noted a paper by Dmochowski et al (Urology. 2003 Aug;62(2):237-42.) which reported the results of study 011, a comparison of transdermal oxybutynin (n = 121) with tolterodine (n = 123) and placebo (n = 117) in patients previously treated with antimuscarinic agents. Members noted that the results of this study indicated that oxybutynin patches have comparable efficacy to long-acting tolterodine.
- 18.9 The Committee noted that there were no head-to-head studies comparing oxybutynin patches with solifenacin, but considered that the available data indicate that solifenacin may be better tolerated than oxybutynin patches as indicated by long term persistence data..
- 18.10 Members noted that the use of oxybutynin patches involves a trade-off between anticholinergic effects and application site reactions. Members noted that application site reactions may be able to be minimised by rotation of application sites.
- 18.11 The Committee noted the NDC Health 2005 slides for Watson Pharmaceuticals, which indicated that the long-term persistence with oxybutynin patches is worse than with all forms of oral oxybutynin.
- 18.12 Members expressed concern about the long-term adhesion of patches that are to be worn for multiple days, and noted a lack of information regarding this such as instructions for when the wearer needs to bath or shower.
- 18.13 The Committee noted that oxybutynin patches are significantly more expensive compared with oral oxybutynin. The Committee noted that PHARMAC had undertaken a cost-utility analysis on oxybutynin patches and solifenacin compared with placebo in patients who are intolerant to oral oxybutynin. The Committee noted that the cost per quality-adjusted life year (QALY) was relatively high compared with other funding proposals.
- 18.14 The Committee considered that the oxybutynin ER preparation may have advantages compared to oxybutynin immediate release preparation due to reduced frequency of administration and reduced side effect profile. The committee requested that PHARMAC staff investigate the possibility of sourcing oxybutynin ER preparation.
- 18.15 The Committee considered that there is an unmet need for younger people with disabling overactive bladder who are intolerant to oxybutynin. The Committee considered that it is desirable to have another agent available for these patients as a second line agent. Different chemical compound such as tolterodine or solifenacin might be more desirable in these patients.
- 18.16 The Committee **recommended** listing oxybutynin patches in the Pharmaceutical Schedule, and recommended this with a low priority.
- 18.17 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*

## **19 Iodine for pregnant and breastfeeding mothers**

- 19.1 The Committee reviewed an application from the Ministry of Health for the listing of an iodine supplement on the Pharmaceutical Schedule for the treatment of iodine deficiency in pregnant and breastfeeding women. The Committee noted letters of support from the Nutrition Department at Otago University, the New Zealand Society of Endocrinology, and the Joint Foods Standards.
- 19.2 The Committee noted that iodine deficiency and goitre was endemic in New Zealand until the iodisation of salt and the use of iodine containing sanitisation agents by the dairy industry. However, the Committee also noted that since the early 1990's iodine dietary intake has reduced, presumably due to a reduction in salt intake and the switch to non-iodine containing agents by the dairy industry.
- 19.3 The Committee noted several New Zealand studies including Thomson et al (2001), Skeaff et al (2005), Mulrine et al (2005) and Pettigrew-Porter et al (2006), which suggest that New Zealand pregnant and breastfeeding women and their infants are at least mildly if not moderately iodine deficient. The Committee noted that none of the New Zealand studies investigated the effect of mild-to-moderate iodine deficiency on pregnancy outcomes and child development in New Zealand.
- 19.4 The Committee noted that the consequences of mild-to-moderate iodine deficiency in pregnancy are not as clear as those of severe iodine deficiency; however, they are likely to include sub-optimal neurological development and delayed psychomotor development.
- 19.5 The Committee noted that the World Health Organisation suggests a recommended dietary intake (RDI) for iodine in pregnant and breastfeeding women of 250 mcg/day and that this is similar to the Australian and New Zealand guidelines of 220 mcg/day in pregnancy and 270 mcg/day for breastfeeding.
- 19.6 The Committee considered that the current salt iodisation programme was not sufficient for pregnant and breastfeeding women and despite the upcoming mandatory fortification of bread with iodine, pregnant and breastfeeding women and their infants could still be at risk of iodine deficiency.
- 19.7 The Committee noted that Mulrine et al (2005) studied the effects of daily 75 mcg and 150 mcg iodine supplements versus placebo in a six month randomised double blind intervention trial in 109 breastfeeding women. The Committee noted that while maternal urinary iodine concentrations, breast milk concentrations and infant urinary iodine concentrations were higher in women receiving the supplements, maternal iodine status still did not reach the recommended levels.
- 19.8 The Committee noted that the American Thyroid Association recommends a supplement of 150 mcg of iodine daily in pregnancy and breastfeeding, although this is not universal as a 200 mcg supplement is also being used internationally. The Committee also noted that the World Health Organisation recommends a daily potassium iodine tablet supplement or a single annual oral dose of 400 mg of iodised oil for these populations.
- 19.9 The Committee considered the potential for iodine toxicity and considered that the relatively small risk of iodine excess is outweighed by the greater risks of iodine deficiency.

- 19.10 The Committee noted the association between selenium and iodine deficiency and that it may be appropriate that selenium supplementation is also considered for pregnant and breast feeding women.
- 19.11 The Committee noted that there were 64,000 live births in New Zealand in 2007 and considered that if all women took iodine tablets for at least three months then this would result in significant expenditure.
- 19.12 The Committee noted that the application was for a tablet containing only iodine. The Committee noted that there is a lack of tablets that contain iodine only but there are a number of tablets that contain iodine in addition to other vitamins and minerals. The Committee considered that either type of tablet was appropriate as long as the tablet does not contain anything that is contraindicated in pregnancy or breast feeding.
- 19.13 The Committee **recommended** that a tablet containing an iodine dose of 150 mcg to 200 mcg be listed on the Pharmaceutical Schedule with a high priority for pregnant and breast feeding women.
- 19.14 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; and (iv) The clinical benefits and risks of pharmaceuticals.*