

PTAC meeting held 5 & 6 May 2011

(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 or PHARMAC staff proposal 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.

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1 Record of PTAC meeting held February 2011

- 1.1 The Committee reviewed the minutes of the PTAC meeting held on 17 & 18 February 2011, and made the following minor amendments:
- 1.1.1 Pazopanib (Votrient) – paragraph 2.6 replace: “The Committee noted that patients reported adverse events in the pazopanib arm” with “The Committee noted that patients reported more adverse events in the pazopanib arm”.
 - 1.1.2 Mycophenolate mofetil – paragraph 6.2 replace: “mycophenolate mofetil may be used to treat patients with severe, treatment-resistant atopic eczema” with “mycophenolate mofetil may be used to treat patients with severe, treatment-resistant atopic eczema under the current Special Authority”.
 - 1.1.3 Mycophenolate mofetil – paragraph 6.7 replace: “five patients had a 60-90% improvement and one patient had an adequate response” with “five patients had a 60-90% improvement and one patient had an inadequate response”.
 - 1.1.4 Clodronate (Ostac) – paragraph 10.4 replace: “The Committee considered that the evidence supporting the efficacy of hyperbaric oxygen is weak” with “The Committee considered that there was no evidence to support efficacy of hyperbaric oxygen and it may be harmful”.

2 Subcommittee minutes

- 2.1 Diabetes Subcommittee Minutes – 3 March 2011
- 2.1.1 The Committee noted the Subcommittee’s recommendation that PHARMAC fund blood glucose test strips for patients with a genetic or an acquired disorder of glucose homeostasis not including type 1 or 2 diabetes or metabolic syndrome, and **recommended** including the words ‘at risk of hypoglycaemia or hyperglycaemia’.
 - 2.1.2 The Committee noted that it would be reviewing insulin pumps later this meeting and would review the Subcommittee’s insulin pump recommendations at that stage.
 - 2.1.3 The remainder of the record of the meeting was noted and accepted.
- 2.2 Ad-hoc Rheumatology Subcommittee Minutes – 8 March 2011
- 2.2.1 The Committee noted that the Subcommittee had recommended amending criterion 2.4.1 of the Special Authority criteria for adalimumab and etanercept in psoriatic arthritis as follows (deletion in strikethrough, addition in bold):

2.4.1 Patient has persistent symptoms of poorly controlled and active disease in at least ~~20~~ **10** active, swollen, tender joints;

The Committee considered that there was no compelling evidence to support this change and instead **recommended** the following change to the Special Authority criteria (deletion in strikethrough, addition in bold), noting that this more closely reflected the patient populations in the clinical trials:

2.4.1 Patient has persistent symptoms of poorly controlled and active disease in at least ~~20~~ **15** active, swollen, tender joints;

2.2.2 The remainder of the record of the meeting was noted and accepted.

3 Mycophenolate for lupus nephritis

Application

3.1 The Committee reviewed a PHARMAC staff proposal prompted by e-mail correspondence from a clinician for the funding of mycophenolate mofetil (MMF) on the Pharmaceutical Schedule to be widened to include induction and maintenance treatment of patients with lupus nephritis (LN) or Vasculitis.

Recommendation

3.2 The Committee **recommended** MMF should be funded for induction treatment in LN or Vasculitis patients who have failed to respond to cyclophosphamide or in whom cyclophosphamide use is not tolerated or is contraindicated. The Committee gave the recommendation for LN patients a high priority and the recommendation for Vasculitis patients a low priority.

3.3 The Committee **recommended** that the Special Authority criteria for MMF should be amended as follows (changes in bold and strikethrough):

Mycophenolate mofetil - Special Authority for Subsidy

Initial application – (Lupus Nephritis and Vasculitis Induction) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist.

Approvals valid for 8 months for applications meeting the following criteria:

All of the following:

1 Either:

1.1 The patient has newly diagnosed active proliferative (class III/IV) and/or membranous (class V) lupus nephritis, or

1.2 The patient has newly diagnosed ANCA-associated Vasculitis; and

2 Either:

2.1 Cyclophosphamide has been trialled and discontinued because of unacceptable side effects or inadequate clinical response; or

2.2 Cyclophosphamide treatment is contraindicated; and

3 Mycophenolate induction treatment to be given in combination with corticosteroids for a maximum of 24 weeks.

Initial application – **Other Diseases** – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:

Either:

1 Transplant recipient; or

2 Both:

Patients with diseases where:

2.1 Steroids and azathioprine have been trialled and discontinued because of unacceptable side effects or inadequate clinical response; and

2.2 Either:

Patients with diseases where:

2.2.1 Cyclophosphamide has been trialled and discontinued because of unacceptable side effects or inadequate clinical response; or

2.2.2 Cyclophosphamide treatment is contraindicated.

- 3.4 The Committee **recommended** that PHARMAC seek further advice from the New Zealand Rheumatology Association and the National Renal Advisory Board regarding the potential number of patients who would be treated with MMF as recommended.
- 3.5 The Committee **recommended** that the funding of MMF for maintenance treatment in LN or Vasculitis patients be declined.

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.*

Discussion

- 3.6 The Committee noted that MMF is not registered for use in patients with LN or Vasculitis. Members noted that MMF is currently funded under Special Authority for use in any disease (including LN or Vasculitis) following failure or discontinuation of corticosteroids, azathioprine and cyclophosphamide or corticosteroids and azathioprine in patients for whom cyclophosphamide is contraindicated.
- 3.7 The Committee noted that in his e-mail the clinician considered it inappropriate that azathioprine should be trialled prior to accessing funded MMF in patients with LN or Vasculitis. Members reviewed evidence in the form of three abstracts provided by the clinician and a number of published studies provided by PHARMAC staff.

Lupus Nephritis

- 3.8 The Committee noted that LN is an inflammatory condition of the kidney that is a complication of the autoimmune disease systemic lupus erythematosus (SLE). Members noted that SLE and LN are more prevalent in Māori, Pacific people, Asians and other races with pigmented skin. Members were uncertain of how many patients with LN would require induction and maintenance treatment per annum and considered that it may be

difficult to forecast patient numbers accurately as these patients are treated by both rheumatologists and nephrologists.

- 3.9 The Committee reviewed evidence for the use of MMF in induction of remission in LN from three meta-analyses, one randomised controlled study (RCT) comparing MMF with azathioprine and one RCT comparing MMF with intravenous (IV) cyclophosphamide.
- 3.10 The Committee noted that the authors of the meta-analyses, which included data from five to 10 trials, concluded that MMF had similar efficacy to cyclophosphamide but with a better safety profile.
- 3.11 The Committee noted that one key study for this indication was a 2-phase (induction and maintenance) randomised controlled study, comparing MMF with IV cyclophosphamide (both in combination with prednisone) in patients with grades 3-5 LN, carried out by the Aspreva Lupus Management Study group (ALMS) (Appel et al 2009). Members noted that this is the largest (370 patients) and latest study to be published in this setting. Members noted that the study failed to meet its primary objective of showing that MMF induction therapy was superior to cyclophosphamide in terms of pre-specified decreases in urine protein/creatinine ratio and stabilisation or improvement in serum creatinine. Members noted that there was no significant difference in response rates between the two groups with 56% of MMF patients responding compared with 53% of cyclophosphamide patients. The study did not detect any significant differences between the groups with regard to rates of adverse events, serious adverse events, or infections.
- 3.12 The Committee considered that overall there was no clinically relevant efficacy or safety difference between induction treatment with MMF or IV cyclophosphamide. Members considered that cyclophosphamide remained the standard of care induction treatment for patients with LN, however, MMF may be a preferred option in patients with moderate disease, those that would prefer an oral treatment and women of child bearing age where cyclophosphamide could be considered contraindicated.
- 3.13 The Committee noted one key open label study comparing induction with azathioprine or cyclophosphamide, followed by azathioprine maintenance therapy, in 87 patients with proliferative LN (Grootscholten et al 2006; Grootscholten et al 2007). Members noted that after a median follow-up of 5.7 years more patients in the azathioprine group (16.2%) had met the primary endpoint of a doubling of serum creatinine compared with those treated with cyclophosphamide (4%), however, neither this primary endpoint, nor relevant secondary endpoints demonstrated any statistically significant difference between the two treatments. Members considered that the study design was poor as it was underpowered, had unbalanced treatment protocols and relatively short term follow-up.
- 3.14 The Committee considered that there was scant evidence for the use of azathioprine as an induction agent in patients with LN. Members considered that azathioprine may have a limited role as an induction treatment in pregnancy or women of child bearing age and in low risk patients. However, members considered overall that there was a lack of evidence to support the use of azathioprine as an induction treatment prior to cyclophosphamide or MMF.

- 3.15 The Committee reviewed evidence for the use of MMF as maintenance therapy in LN comprising two meta-analyses and two RCTs comparing MMF with azathioprine in this setting.
- 3.16 The Committee noted that in the second phase of the ALMS study (Ginzler et al 2010), patients were randomised to maintenance treatment with MMF or azathioprine. Members noted that MMF maintenance was statistically superior to azathioprine in time to treatment failure, time to rescue therapy and time to first confirmed or suspected renal flare, but not time to End Stage Renal Disease or other secondary endpoints and results were consistent regardless of induction treatment (MMF or IV cyclophosphamide). Members also noted no significant difference in safety between the two treatments.
- 3.17 The Committee reviewed evidence from a second RCT, the MAINTAIN study, comparing maintenance treatment with MMF or azathioprine in 105 patients (Houssiau et al 2010), which found no statistically significant differences between the two groups for efficacy or safety endpoints.
- 3.18 The Committee considered that overall MMF and azathioprine had similar efficacy and safety outcomes when used for maintenance of remission in patients with LN, and that the optimal maintenance treatment remains to be established.

Vasculitis

- 3.19 The Committee noted that the term Vasculitis covers a range of conditions that affect the small, medium and large blood vessels.
- 3.20 The Committee reviewed evidence from one key RCT comparing maintenance therapy with MMF or azathioprine, two retrospective studies of MMF in induction and European League Against Rheumatism (EULAR) recommendations for the management of primary small and medium vessel vasculitis.
- 3.21 The Committee noted that the EULAR guidelines (Mukhtyar et al 2009) recommend cyclophosphamide induction treatment in combination with steroids and methotrexate plus steroids as a less toxic alternative in non-organ or life-threatening vasculitis. The guidelines recommend azathioprine, methotrexate or leflunomide as maintenance therapy. Members further noted that the guidelines recommend that MMF should be considered in patients who do not achieve remission, or who relapse, on maximum doses of standard therapies.
- 3.22 The Committee noted that the two retrospective studies (Koukoulaki and Jayne 2006, Stassen et al 2007) were small single arm studies; however, they did appear to show that patients responded to MMF treatment although the responses did not seem to be maintained with approximately half of all patients who initially responded relapsing. Members noted that there were no RCTs comparing MMF with other treatments in the induction setting. Members considered that MMF may be a reasonable induction option in patients who failed to respond to induction treatment with cyclophosphamide, or in whom cyclophosphamide is not tolerated or use was contraindicated.
- 3.23 The Committee reviewed evidence from a recent, randomised controlled study, the IMPROVE study (Heimstra et al 2010) that compared maintenance treatment with MMF or azathioprine in 156 patients with Vasculitis (Wegener's granulomatosis or microscopic

polyangiitis) positive for Anti-Neutrophil Cytoplasmic Autoantibody (ANCA) following induction treatment with cyclophosphamide and steroids. Members noted after a median follow-up of 39 months, relapses were more common in the MMF group (55%) compared with the azathioprine group (37.5%), (HR 1.69 ,95% CI, 1.06-2.70; P=.03).

- 3.24 The Committee considered that overall there was no evidence to suggest that MMF offers any safety or efficacy benefit over azathioprine when used for maintenance of remission in patients with Vasculitis.

4 Rituximab (Mabthera) for maintenance treatment in relapsed/refractory follicular non-Hodgkin's lymphoma

Application

- 4.1 The Committee reviewed an application from Roche Products (NZ) Ltd for funding of rituximab (MabThera) on the Pharmaceutical Schedule to be widened to include maintenance treatment in patients with relapsed/refractory follicular Non-Hodgkin's Lymphoma (NHL).

Recommendation

- 4.2 The Committee **recommended** that the application be deferred pending longer term data from relevant studies becoming available. The Committee further **recommended** that the application be referred to its Cancer Treatments Subcommittee for consideration.

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.*

Discussion

- 4.3 The Committee noted that rituximab is currently funded for remission induction treatment in patients with indolent low grade NHL, aggressive CD20 positive NHL, B-cell post transplant lymphoproliferative disorders and relapsed disease where patients have had a treatment free period of 12 months or more.
- 4.4 The Committee noted that relevant evidence in support of the funding proposed comprised one open-label randomised controlled study from the European Organisation for Research and Treatment of Cancer (EORTC 20981, Van Oers et al Blood 2006 108:3295-3301; Van Oers et al J Clin Oncol 2010;28:2853-2858).
- 4.5 The Committee noted that EORTC 20981 enrolled 465 adult good performance status (ECOG 0-2) patients with CD20-positive, grade 1–3 follicular NHL, Ann Arbor stage III or

IV at initial diagnosis, who had relapsed after / resistance to a maximum of two non-anthracycline containing systemic chemotherapy regimens. Members noted that exclusion criteria included any previous therapy with anthracyclines and/or rituximab, autologous or allogeneic stem cell transplantation and patients with histological transformation to aggressive NHL.

- 4.6 The Committee noted that patients underwent two randomisations: initially patients were randomised (1:1) to receive six cycles of remission induction treatment with CHOP or R-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone with or without rituximab). After three cycles of treatment, patients who experienced stable disease or disease progression were removed from the study. Patients who were responding to treatment received another three cycles and those who achieved a complete or partial response (CR or PR, respectively) underwent a second randomisation (1:1) to observation (no further treatment) or maintenance treatment which comprised rituximab 375 mg/m² once every three months until relapse or for a maximum of two years. Members noted of the 336 patients who responded to induction treatment, 334 were eligible for second randomisation.
- 4.7 The Committee noted that after a median follow-up of six years, rituximab maintenance significantly improved Progression Free Survival (PFS) compared with observation (median PFS 3.7 years vs 1.3 years; P <0.001; hazard ratio [HR], 0.55), both after CHOP induction treatment (median, 3.1 years vs 1 year; P <0.001; HR, 0.37) and R-CHOP induction treatment (median, 4.4 years v 1.9 years; P <0.003; HR, 0.69). However, members noted that at five years there was no statistically significant difference in Overall Survival (OS) between the two groups with 74.3% of patients alive in the rituximab maintenance arm compared with 64.7% in the observation arm (HR 0.70, 95% CI 0.48-1.03, P =0.07). Members considered that this may have been due to unbalanced use of rituximab in the post-protocol salvage setting.
- 4.8 The Committee noted that patients treated with rituximab had a higher incidence of grade 3/4 neutropaenia (11.5% vs 6%) and more grade 3/4 infections (9.7% vs 2.4%) mainly ear nose and throat infections.
- 4.9 The Committee considered that the evidence from EORTC 20981 was of good strength and moderate quality, however, members considered that the population enrolled in EORTC 20981 was not representative of the current NHL population in New Zealand. Members considered that currently most NHL patients in New Zealand receive rituximab as a first line treatment and there would be very few patients who were rituximab and anthracycline-naïve at relapse. Members also noted that the median age of patients enrolled in EORTC 20981 was low compared with the NZ NHL population. Because of these issues the Committee were not certain of the applicability of the data to the NZ setting and the appropriate place in therapy for maintenance treatment.
- 4.10 The Committee noted another randomised controlled study had recently been published that addressed the question of the use of maintenance therapy in an earlier setting. Members noted that this study, PRIMA (Salles et al Lancet 2011;377:42-51) enrolled 1217 patients with previously untreated follicular NHL, patients received one of three non-randomised induction regimens and 1019 patients achieving CR or PR were randomised (1:1) to receive two years of rituximab maintenance therapy (375 mg/m² every 8 weeks) or observation. Members noted that the rituximab schedule in this study differed from that in the EORTC 20981 study.

- 4.11 The Committee noted that after a median follow-up of 36 months in the PRIMA trial, rituximab maintenance significantly improved PFS compared with observation, with PFS in 130 patients (74·9%) in the rituximab maintenance group compared with 218 (57·6%) in the observation group (HR 0·55, 95% CI 0·44-0·68, $p < 0·0001$). However OS did not differ significantly between the two groups (HR 0·87, 95% CI 0·51-1·47). Further, members noted that despite improved PFS patients' quality of life was not improved in those receiving rituximab maintenance.
- 4.12 The Committee also reviewed a meta-analysis of five RCTs comparing rituximab maintenance therapy to observation, treatment at relapse only (i.e. no maintenance therapy), or other maintenance treatment (Vidal et al JNCI 2009;101:248-55), and an updated analysis of eight RCTs presented as a poster at the 2010 American Society of Haematology meeting (ASH). Members considered that the trials were heterogeneous for diagnoses, population enrolled and regimens used.
- 4.13 The Committee considered that overall the evidence demonstrated that rituximab maintenance treatment did improve PFS but that no improvement was shown for overall survival or quality of life. Members further considered that there remained several important unanswered questions regarding the optimal use of rituximab maintenance therapy, including the optimal schedule and duration of rituximab maintenance treatment, its place in the treatment algorithm for patients with NHL and the role of maintenance treatment compared with treatment at relapse. Members noted that studies to address some of these questions were ongoing or planned.

5 Ustekinumab (Stelara) for psoriasis

Application

- 5.1 The Committee reviewed an application from Janssen-Cilag (New Zealand) Limited for the listing of ustekinumab (Stelara) on the Pharmaceutical Schedule for the treatment of patients with severe chronic plaque psoriasis.

Recommendation

- 5.2 The Committee **recommended** that ustekinumab be listed on the Pharmaceutical Schedule under Special Authority only if cost neutral to other funded biologics.
- 5.3 The Committee **recommended** that the 90 mg dose be considered for funding only if cost neutral to the 45 mg dose.
- 5.4 The Committee **recommended** that a limit of two biologic therapies be included as part of a Special Authority.

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;* 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.

Discussion

- 5.5 The Committee noted that ustekinumab had a different mechanism of action to other biologics as it reduced differentiation and clonal expansion of implicated Th1 and 17 subsets in comparison with etanercept and adalimumab which act to inhibit the action of the TNF alpha produced by these Th1 and 17 cells.
- 5.6 The Committee reviewed the PHOENIX 1 (Leonardi et al Lancet 2008;371:1665-674; Lebwohl et al Br. J. Dermatol 2010;162:137-146) and PHOENIX 2 (Papps et al Lancet 2008;1675-1684; Langley et al J Am Acad Dermatol 2010;63:457-465) studies and the Lebwohl et al (J Am Acad Dermatol 2010;63:571-579; version supplied in press) study on dosing recommendations. The Committee noted that the PHOENIX 1 and 2 studies were randomised double blind placebo controlled trials where the principal clinical endpoint was the proportion of patients achieving a Psoriasis Area Severity Index score 75% or less of baseline (PASI 75). Treatment with ustekinumab resulted in significant improvements in PASI scores and also quality of life measurements. PASI 75 at 12 weeks was achieved in approximately 67% of those on the 45 mg dose and 66-75% of those on the 90 mg dose.
- 5.7 The Committee reviewed the Igarashi et al study (Poster; 3rd International Congress of the Psoriasis International Network, Paris, 2010). Members noted this was a randomised trial comparing placebo against ustekinumab 45 mg or 90 mg. Members noted that at week 12, 59.4% of patients on 45 mg and 67.7% of patients on 90 mg achieved a PASI 75.
- 5.8 The Committee reviewed the ACCEPT study (Griffiths et al N Engl J Med 2010;362:118-28), a randomised active controlled trial comparing ustekinumab 45 mg and 90 mg with etanercept 50 mg. Members noted that the etanercept dosage in the study was 50 mg twice weekly and that etanercept was only funded for 50 mg once weekly in New Zealand. At week 12, 67.5% of patients on 45 mg and 73.8% of patients on 90 mg of ustekinumab had achieved PASI 75 compared to 56.8% of etanercept patients, which was statistically significant.
- 5.9 The Committee considered that the patient weight-based subgroup analysis (Lebwohl 2010, above), which had been presented to justify the 90 mg dose of ustekinumab for patients weighing greater than 100 kg was poor. The Committee considered that this subgroup analysis did not test or report for statistical interaction between patient weight and ustekinumab dose, and was of lesser validity and poor quality. In particular, members noted that:
- 5.9.1 The Lebwohl paper reported the primary exposure categories in the subgroup analysis to be 10-kg patient weight-bands (across ustekinumab dosages), but that there was no description of the planned statistical methods to analyse these continuous categorical variables, nor reporting of any results including reporting for a statistically significant effect for this primary exposure categorisation;

- 5.9.2 Although the Lebwohl paper reported the additional analyses of dichotomous (binary) variables (less than 100 kg, greater than 100 kg), the delineation between these weights appeared to have been arbitrarily selected post-hoc without a described prospective statistical analysis plan to manage and measure dichotomous (rather than continuous) variables;
- 5.9.3 The reasoning in the Lebwohl paper for selecting 100 kg as the weight to delineate dichotomous weight-based groups was not strong, and it would have been equally appropriate, for example, to prospectively select mean or median weights to delineate the two weight-based groups; and
- 5.9.4 Although the Lebwohl paper presented results of further post-hoc dichotomous analyses that attempted to control for confounding variables across the two comparisons, it did not present the methods nor the underlying contributing data.
- 5.10 Members also noted that the mean weight of all ustekinumab patients in the PHOENIX 1 and 2 trials combined was close to 90 kg, and that this would have divided the dichotomous patient weight-based subgroup analysis (Lebwohl) into patients weighing less than 90 kg vs. greater than 90 kg. Members considered that adjusting the dichotomous patient weight categories would affect any future estimates of statistical interaction.
- 5.11 The Committee therefore considered that the evidence presented in the weight-based subgroup analysis did not justify the higher dose and recommended that the 90 mg dose be considered for funding only if cost neutral to the 45 mg dose. Members noted the high correlation between body mass and incidence and potential severity of psoriasis identified at the 2006 International Psoriasis Council meeting.
- 5.12 The Committee noted there was limited safety data to 18 months for ustekinumab in the Phoenix 1 and 2 studies and 65 weeks in the ACCEPT study. Members noted that the adverse event profile was similar to etanercept over this time period. Members considered that there was a potential carcinogenic risk with biological therapy and as ustekinumab was a first in class treatment there was a less clear long-term safety profile. The Committee considered that ustekinumab should be a mandatory inclusion in the Intensive Medicines Monitoring Programme (IMMP). The Committee further considered that PHARMAC staff should write to MedSafe regarding its comments about IMMP monitoring.
- 5.13 The Committee noted that ACCEPT data suggested that those who fail on etanercept may achieve a response with ustekinumab with approximately 50% of patients showing a PASI 75 after three doses. Members considered that two biological therapies for treatment of psoriasis would be appropriate and recommended that a limit of two biologic therapies be included as part of a Special Authority.
- 5.14 The Committee noted that ustekinumab required 12 weekly injections which may improve compliance compared to other funded biological therapies.
- 5.15 The Committee considered that assessment of treatment should occur after three doses of ustekinumab, between weeks 16 and 28 of therapy. Members noted that therapy should be discontinued if there was no response after 16 weeks of therapy.

6 Montelukast for pre-school wheeze

Application

- 6.1 The Committee reviewed a PHARMAC staff proposal for the listing of montelukast on the Pharmaceutical Schedule for the treatment of pre-school wheeze.

Recommendation

- 6.2 The Committee **recommended** that montelukast be listed in the Pharmaceutical Schedule under Special Authority with a low to medium priority.
- 6.3 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 Māori 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (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

- 6.4 The Committee noted that in July 2010 the Respiratory Subcommittee had recommended montelukast be listed for the treatment of pre-school wheeze under a Special Authority restricting use to children aged four years and under with intermittent severe wheezing who had undergone a trial of inhaled corticosteroids and had a history of three exacerbations within the previous 12 months, one of which required hospitalisation (defined as intensive treatment in an E.D or after hours medical centre or an overnight stay in hospital).
- 6.5 The Committee noted that there are at least five different phenotypes of wheezing in pre-school children and that there is difficulty in the identification of the specific phenotype affecting a child. This leads to difficulty in utilising appropriate treatments in the very young. The five different phenotypes were identified as persistent cough; transient cough; atopic persistent wheeze, non-atopic persistent wheeze and transient viral wheeze (Spycher et al Eur Resp J 2008;31:974-981) and that older suggestions have been episodic (viral) wheeze and multiple trigger wheeze (Brand et al Eur Resp J 2008;32:1096-1110). The Committee noted that children may change between phenotypes across childhood and that two-thirds of children with wheezing in the first three years of life were no longer wheezing at age six.
- 6.6 The Committee noted that in addition to the problems associated in distinguishing between the different wheezing phenotypes, the association of the expanding group of phenotypes with bronchiolitis is unresolved. The Committee noted that the American Association of Paediatrics defines bronchiolitis as symptoms and signs of respiratory distress (tachypnoea, recession, nasal flaring, and cyanosis) associated with symptoms of a viral respiratory tract infection (cough, runny or blocked nose). The Committee noted

that bronchiolitis is due to viral infection, 70% of which are from Respiratory Syncytial Virus (RSV), that bronchiolitis tends to occur in children aged less than one year old but it can occur in the second year of life, and that the current recommended treatment is supportive.

- 6.7 The Committee reviewed the Bisgaard et al (Am J Respir Crit Care Med 2008;178:854-60) study. Members noted this was a multi-centre double blind randomised controlled trial (RCT) (n = 979) comparing montelukast (4 mg or 8 mg) vs placebo for four weeks with a 20 week extension period in children age three to 24 months who were hospitalised for 24 hours with a first or second episode of physician diagnosed RSV-positive bronchiolitis. The primary outcome was the percentage of days symptom-free in the first four weeks of treatment. Members noted that there was no difference between the groups, although a post hoc exploratory analysis, subject to bias, suggested a small benefit from treatment with montelukast. The Committee noted that this trial reflects a different patient population to that suggested in the application, as 75% of the trial patients were aged less than one year old, the trial excluded those with two or more episodes (therefore not recurrent episodes of wheeze), and all participants had to be RSV positive – where in practice RSV accounts for only a small percentage of those with viral induced wheeze aged over one year.
- 6.8 The Committee reviewed two double blind randomised controlled trials of intermittent use in an acute setting – Robertson et al (Am J Respir Crit Care Med 2007;175:323-329) and Bacharier et al (J Allergy Clin Immunol 2008;122:1127-1135).
- 6.9 The Committee noted that Robertson et al (n=220) evaluated parent-initiated montelukast 4 mg or 5 mg vs placebo at the onset of asthma symptoms or upper respiratory tract infections (URTIs) for seven days or until symptom free for 48 hours with a maximum of 20 days treatment. Members noted that the inclusion criteria were children aged two to 14 years with doctor-diagnosed intermittent asthma (three to six episodes in the past 12 months with one hospital admission or ED visit and two or more GP visits in the past 12 months). The outcome measures were acute health visits for asthma, episode duration, total daily symptom score, SABA use, oral steroid use, parental days off work, nights with disturbed sleep and days absent from school or pre-school. The Committee noted that 40% of placebo episodes resulted in acute visits vs 30% for montelukast (rate reduction 0.65, 95% CI 0.47-0.89, p=0.008); montelukast resulted in a reduction in total symptom scores (p=0.049), fewer days away from school/pre-school/work (p=<0.0001), less disturbed nights (p=0.043), but no change in the duration of episodes.
- 6.10 The Committee noted that Bacharier et al (n=238) compared seven days treatment with montelukast 4 mg od vs budesonide 1 mg bd vs placebo in addition to salbutamol use with each identified respiratory tract illness. Inclusion criteria were children aged 12 to 59 months with more than two wheeze episodes in the past 12 months, two of which required urgent care and/or oral steroids. Members noted that there was no difference in the proportion of episode free days, oral steroid use, acute care use, quality of life or adverse events however symptom severity was decreased during acute respiratory tract illness.
- 6.11 The Committee noted that Knorr et al (Paediatrics 2001;108:e48.) was a double-blinded RCT of montelukast 4 mg vs placebo for 12 weeks with the inclusion criteria of children aged two to five years who had three episodes of asthma symptoms during the previous

year requiring the use of a bronchodilator. Members noted that use of montelukast reduced daytime asthma symptoms ($p=0.012$) and the use of bronchodilators ($p=0.001$) and increased the number of days without asthma ($p=0.002$) compared to placebo. Members noted that this small benefit was in patients with moderate disease whose phenotype was closer to asthma than intermittent pre-school wheeze associated with viral infections and is similar in efficacy to inhaled corticosteroids.

- 6.12 Members noted that Szeffler et al (J Allergy Clin Immunol 2007;120:1043-50.) was an open label randomised active control study comparing montelukast 4 mg with budesonide 0.5 mg nebulas for 52 weeks enrolling 395 children aged two to eight years with mild persistent asthma or children with more than three wheezing episodes. Members noted that there was no significant difference in the primary endpoint of time to additional treatment ($p=0.29$) however the budesonide group showed a slight benefit in exacerbations per subject per year, and peak flow and Global assessments favoured budesonide. Members noted that the study looked at a mild to moderate population which gave limited opportunity for improvements and that the study was sub-optimal in terms of primary end-point, lack of discontinuation criteria and step-up design.
- 6.13 The Committee noted that Bisgaard et al (Am J Respir Crit Care Med 2005;171:315-322) was a double blinded RCT of montelukast 4 mg vs placebo for 12 months in children 2-5 years ($n=549$) with intermittent asthma (characterized by the absence of symptoms and SABA use in a typical week over three months before the trial) resulting from a URTI. Members noted that in the montelukast arm there was a significant reduction in asthma episodes ($p<0.001$), a reduction in the overall rate of corticosteroid use ($p=0.024$), a longer time to the first exacerbation ($p=0.024$) and the proportion of participants with asthma exacerbations reduced ($p=0.008$). Members noted that there were low rates of hospitalization overall (4.2% vs 5.8%), the duration and severity of episodes were similar between the groups and that the episode free days tended to favour montelukast.
- 6.14 Members noted that Johnson et al (Pediatrics 2007;120:e702-e712) was a double blind RCT of montelukast (4 mg or 5 mg od) vs placebo for 45 days following return to school in 194 children aged two to 14 years, 90% of whom had been prescribed an ICS. Members noted that there was an overall reduction in worse asthma days ($p<0.02$) and a 78% reduction in unscheduled healthcare visits ($p=0.011$) in the montelukast group. Members noted that, overall for the study group, those taking regular ICS showed a significant effect (adjusted OR:0.13; 95% CI: 0.03-0.51).
- 6.15 In terms of alternate treatment, members noted that there were no direct head-to-head trials presented comparing montelukast with other treatments in childhood wheeze. Members noted that oral prednisone is poorly efficacious in exacerbations of wheeze in pre-school children, with two placebo-controlled RCTs showing no effect of treatment (Oommen et al Lancet 2003;362:1433-38; Panickar et al N Engl J Med 2009;360:329-38) and a Cochrane review (McKean & Ducharme Cochrane database Syst Rev 2000;Issue 1:CD001107) showing no evidence for the use of ICS maintenance therapy on outcome although there was some evidence for episodic high dose ICS reducing the need for oral steroids. Members noted that the Cochrane review was over 10 years old and included only one small trial of pre-school children using ICS maintenance therapy.
- 6.16 Members noted two further recent studies: Bisgaard et al (Pediatrics 2004;113:e87-e94), an open label RCT with 625 children aged one to three years with recurrent cough and wheeze comparing fluticasone (100 mcg bd) vs sodium cromoglycate (5 mg qid), which

reported fluticasone to be more effective and having no effect on growth; and Durcharme et al (N Engl J Med 2009;360:339-353.), a triple-blind RCT of fluticasone (750 mcg bd) vs placebo for up to 10 days for the treatment of viral infections in children aged one to six years who had previously had wheeze associated with URTIs, which reported that pre-emptive treatment with fluticasone reduced the use of rescue oral corticosteroids but was associated with a smaller gain in height and weight.

- 6.17 The Committee noted that there is a very high burden of disease in children with pre-school wheeze and respiratory related admissions to hospital for pre-schoolers is five times the admission rate for adults. Members noted that few pharmaceuticals work well in this area.
- 6.18 Members considered that the evidence of efficacy for the use of montelukast in pre-school children is modest to poor, that the quality of the RCTs is modest, and that there is heterogeneity among the treatment groups (reflecting both the difficulty in positively identifying patient phenotypes and patients sometimes changing phenotypes with age). Members noted that in persistent asthma there is moderate evidence that montelukast reduces symptoms compared with placebo to a similar extent to budesonide, and that in intermittent asthma associated with URTIs the regular use of montelukast reduces asthma episodes and the use of steroids.
- 6.19 Members noted that montelukast would most likely be used in combination with SABAs and oral steroids and that it would be of benefit to pre-schoolers with intermittent or persistent asthma, particularly wheeze associated with viral URTIs in children who are over 12 months of age. Members noted that an oral treatment offers benefits to some families who find giving inhaled medications a struggle, particularly in young children.
- 6.20 The Committee considered the draft Special Authority changes as follows, and **recommended** that the Committee review the changes at its next meeting (changes in strike through and bold):

Initial application from any relevant practitioner only from a paediatrician
Approvals valid for ~~three months~~ one year for applications meeting the following criteria:

All of the following:

- 1 To be used for the treatment of intermittent severe wheezing (possibly viral) in children under ~~4~~ **5** years; and
- 2 The patient has trialled inhaled corticosteroids at a dose of up to 400µg per day beclomethasone or budesonide, or 200 µg per day fluticasone for at least one month; and
- 3 The patient continues to have at least three severe exacerbations at least one of which required hospitalisation (defined as in-patient stay or prolonged Emergency Department treatment) in the past 12 months.

Renewal only from a relevant practitioner. Approvals valid for two years where the treatment remains appropriate and the patient is benefitting from treatment.

- 6.21 Members **recommended** that there should be a restriction on the number of tablets dispensed per prescription as the evidence for the effectiveness of montelukast is strongest when used intermittently.

7 Multiple sclerosis treatments

Application

- 7.1 The Committee reviewed cost-utility analysis (CUA) models provided by PHARMAC staff in relation to previous applications by various parties to widen funded access to the multiple sclerosis (MS) treatments beta-interferon (interferon beta-1-alpha [Avonex] and interferon beta-1-beta [Betaferon]) and glatiramer acetate (Copaxone). The Committee also reviewed a request by members of the Multiple Sclerosis Treatment Assessment Committee (MSTAC) to amend the Stopping Criteria to allow patients to switch class of treatment if they have a stable or increasing relapse rate over 12 months and meet the Expanded Disability Status Scale (EDSS) Stopping Criteria.

Recommendations

- 7.2 The Committee **deferred** re-consideration of its previous recommendation to decline all applications to amend the Entry Criteria for funded access to multiple sclerosis treatments, pending review of its suggested revisions to the CUA to be performed by PHARMAC staff.
- 7.3 The Committee **recommended** that PHARMAC's CUA models continue to assume that baseline relapse rates and EDSS progression are independent.
- 7.4 The Committee **recommended** that the Stopping Criteria not be amended as proposed by MSTAC.

Discussion

- 7.5 The Committee noted that the criteria for funded access to MS treatments were amended on 1 December 2010 to incorporate its previous recommendations to amend the Stopping Criteria and to permit treatment switching in patients with a stable or increasing relapse rate over 12 months of treatment provided that no other Stopping Criteria are met.
- 7.6 The Committee noted that following widening of access, members of MSTAC had requested that the Stopping Criteria be further amended to permit treatment switching in patients with a stable or increasing relapse rate if they also meet the EDSS-related Stopping Criteria because, in MSTAC's view, there is a positive relationship between relapse rates and EDSS progression such that patients with increasing relapse rates will likely also experience an increase in EDSS.

- 7.7 The Committee noted that it most recently considered the application to amend the Entry Criteria in August 2010, when it deferred re-consideration of its previous recommendation to decline all applications to amend the Entry Criteria for funded access to MS treatments pending an updated CUA to be performed by PHARMAC staff for review by the Committee. The Committee noted that PHARMAC staff had modelled several scenarios in the main and supplementary CUAs and sought the Committees advice around assumptions and inputs. The Committee noted that a key assumption in the model was that relapse rates are independent of EDSS progression.

Relationship between relapse rates and EDSS progression

- 7.8 The Committee noted that it had previously considered the relationship between baseline relapse rates and EDSS progression in the natural history of MS at its February 2010 meeting and had considered that the evidence that a reduction in relapse rates leads to a marked reduction in disability progression to be inconsistent and weak.
- 7.9 The Committee re-reviewed several publications (Boggild et al BMJ 2009;339:b4677; Kremenchutzky et al Brain 2006;129:584-94; Ebers J. Neurology 2005 ;252:S15-20; Langer-Gould et al Arch Neurol 2006;63:1686-1691; McDonald N Engl J Med 2000 ;343:1486-7; Mandrioli et al. J Neurology 2008;255:1023-31; Weinshenker et al Brain 1989;112:1419-28) and reiterated its previous view that these publications did not support a positive relationship between baseline relapse rates and EDSS progression.
- 7.10 The Committee noted that it had also previously considered the descriptive report of the UK risk sharing scheme by Pickin et al (BMC Neurology 2009;9:206-13) which reported no relationship between relapse rates and disease progression. Members considered that the point estimate results suggested that those patients with higher baseline rates of relapses (prior to treatment) may have had slower (not faster) rates of disease progression, although such results had not been subjected to testing for statistical significance.
- 7.11 The Committee also considered a more recent publication (Tremlett et al Neurology 2010;74:2004-15), which it considered to emphasise the confusing and weak or non-existent relationship between baseline relapse rates and long-term EDSS progression.
- 7.12 The Committee considered MSTAC's previous view that effective prevention of relapses does lead to progressive improvement in EDSS if no underlying progression is present, based on three sources: data from the NZ funded MS treatment programme, the pivotal treatment trials and the members' personal experience of patients on long-term natalizumab. Taking each point in turn:
- 7.12.1 The Committee noted that it had not been provided with any data or analysis from the MS treatment program and, therefore, was unable to comment on this. The Committee noted, however, that such data would be at the level of evidence of a cohort study with a moderate risk of bias and that it would be unclear whether the relationship was causal.
- 7.12.2 The Committee considered the most recent systematic review and meta-analysis of the beta-interferon trials in relapsing-remitting MS (RR-MS) presented by Rice et al (Cochrane Database of Systematic Reviews 2001, Issue 4:D002002; April 2009). A meta-analysis of outcomes indicated a 9%

absolute risk difference in two-year disease progression rates, and in the two trials that provided information there was evidence at two years of a small difference in EDSS levels (0.25). The Committee noted the Cochrane review's observation that drop-out rates affected the quality of the RCTs. The Committee considered that, as noted in the Cochrane review, the evidence that beta-interferon reduces the EDSS score compared to control treatment is weak and was not reported in most trials. Therefore, the Committee considered that the evidence from the pivotal trials, that on average beta-interferon improves EDSS, is weak. The Committee also noted that the comparative analysis of the UK risk sharing scheme (Boggild et al, BMJ 2009; 339:b4677) reported that patients on average, on treatment deteriorated more rapidly compared with the historical control group.

7.12.3 The Committee noted that it had not previously reviewed any evidence in support of the use of natalizumab for MS. However, the Committee considered that a systematic review of natalizumab (Goodin et al Neurology 2008;71:776) provided relevant information. This review indicated that natalizumab was associated with a lower risk of relapse at two years compared to placebo, with a magnitude of benefit likely to be similar to beta-interferon by informal indirect comparisons and a lower risk of progression by one EDSS point, about the same or a little better than beta-interferon in indirect analyses. In the review no direct link was made between relapse rates and EDSS deterioration (disease progression).

7.13 In summary, the Committee considered that no new evaluable evidence was presented in support of a link between baseline relapse rates and EDSS progression.

7.14 Therefore, the Committee considered that baseline relapse rates and EDSS progression should still be modelled as independent variables in the CUAs, as there was no compelling evidence presented to suggest a relationship between relapse rates and disease progression. The Committee noted that even if there is a causal relationship between relapse rates and EDSS progression, there is no available evidence able to quantify the numerical relationship between the two.

Amending access criteria to allow treatment switching in patients with stable or increasing relapse rates who also meet the EDSS-related Stopping Criteria

7.15 The Committee considered that, as there is currently no compelling evidence to support a positive relationship between relapse rates and EDSS progression, the access criteria should not be amended to permit treatment switching in patients who have a stable or increasing relapse rate over 12 months and who meet the EDSS-related Stopping Criteria.

7.16 However, in reviewing the new (December 2010) EDSS-related Stopping Criteria, the Committee considered that a one point deterioration in EDSS may be insensitive to actual permanent disability change and that it may be reasonable to rescale the Stopping Criteria as follows: 'Confirmed progression of disability sustained for six months during a minimum of one year of treatment defined as: either of (a) an increase of 2 EDSS points where the starting EDSS was 2.0 to 3.5 inclusive (b) an increase of EDSS to 6.0 or greater'. The Committee requested that PHARMAC staff include this scenario in the CUA.

- 7.17 The Committee noted that if the Stopping Criteria were amended in this way, it might be possible for patients to have a stable or increasing relapse rate over 12 months and have a worsening of EDSS score without meeting the EDSS-related Stopping Criteria.

CUA Assumptions and Inputs

- 7.18 The Committee considered the original MS CUA (that assessed the cost-effectiveness of amending Stopping criteria and treatment switching), which included a number of scenarios as previously advised by PTAC, and a new supplementary CUA (that assessed the cost-effectiveness of amending Entry Criteria) which included a number of additional scenarios. Along with not changing the assumption of independence between baseline relapses and baseline EDSS progression, the Committee considered that the assumptions and inputs in the CUAs were reasonable, but noted that although patients with MS do ultimately have an increased mortality compared with people without MS (Ragonese et al Eur J Neurology 2008;15:123-7), there is no evidence that beta-interferon or glatiramer reduce mortality or improve survival.
- 7.19 The Committee considered that there may be some scope for modelling a positive effect on disease progression with treatment switching. The Committee considered that the model should be revised to take into account the probability of response to a second treatment in patients who switch treatments after 12 months being similar to the probability of response to the first treatment. The Committee also suggested modelling a reduced probability of response with EDSS progression from the second treatment compared with the first. The Committee considered this reduced but positive delay in disease progression with treatment switching would be the most reasonable scenario for base case analysis.
- 7.20 The Committee requested that the following scenarios be considered in relation to requests to amend the Entry Criteria: (i) baseline EDSS less than or equal to 5.5 and a baseline annualised relapse rate (ARR) of two or more; (ii) baseline EDSS less than or equal to 2.0 and baseline ARR of three or more; (iii) baseline EDSS of 2.5 to 5.5 and a baseline ARR of two or more.
- 7.21 The Committee considered the scenario that modelled widening access through lowering entry relapse rate thresholds (scenario 1S in the draft supplementary CUA considered by the Committee). The Committee considered that modelling an entry level ARR of one is reasonable but noted that it may be necessary to amend the Stopping Criteria in this model to reflect the lower entry level ARR.
- 7.22 The Committee considered the scenario that modelled widening access by permitting treatment of very early disease (EDSS 0–2) (scenario 4S). The Committee noted that treating MS after the first demyelination episode, but before an absolute MS diagnosis had been made, would risk unnecessarily treating patients without MS. Members agreed with the baseline disease progression and treatment delay assumptions in this scenario, which were based on the median values in the clinical trials.
- 7.23 The Committee considered the scenario that modelled to widening access by raising the Stopping Criterion to EDSS 7.0 (scenario 5S). The Committee considered that treatment at this level of EDSS progression is likely to be slightly less effective, so it would be reasonable to model a shorter time to progression and a higher risk of progression.

- 7.24 The Committee considered the scenario which included secondary progressive MS in the Stopping Criteria (scenario 6S). The Committee considered that this scenario was reasonable, noting that it would be difficult to justify continuing treating patients with secondary progressive MS as the evidence to support beta-interferon and glatiramer efficacy in this group of patients is less robust than the evidence for relapse remitting MS. Members suggested that a model which doubled the deterioration rate to 0.48 EDSS per year as an important sensitivity analysis rather than using the 0.24 per year in this scenario.
- 7.25 The Committee considered that the scenario that modelled treatment switching within a 24 month period rather than a 12 month period without reapplication (scenario 7S) would be difficult to justify without good evidence.

8 Insulin pumps

Application

- 8.1 The Committee reviewed a PHARMAC staff proposal for the funding of Insulin Pumps and Consumables.

Recommendation

- 8.2 The Committee **recommended** that Insulin Pumps and Consumables should be funded under eligibility criteria for patients with type 1 diabetes with a medium priority.
- 8.3 The Committee **recommended** that the application be referred to its Diabetes Subcommittee for consideration and specific advice regarding appropriate eligibility criteria. The Committee further **recommended** that a set of exit criteria should exist which take into account failure to achieve or maintain target HbA1c levels and that patients should be required to complete education and monitoring requirements.

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 Māori 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; (viii) The governments priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC.

Discussion

- 8.4 The Committee noted the application to fund Insulin Pumps and Consumables was for consideration for patients with type 1 diabetes only. Members noted that the only treatment for type 1 diabetes is exogenous insulin, and intensive treatment, designed to prevent future complications, may be complicated by hypoglycaemia, which can be fatal; and patient adherence with intensive treatment regimens may be abated in those patients who suffer serious hypoglycaemic episodes.
- 8.5 The Committee considered the Diabetes Control and Complications Trial (DCCT) (J Diabetes Complications 1993;7:214-5) which the Diabetes Subcommittee had

considered to be the seminal trial for type 1 diabetes. The trial randomised, in the primary prevention arm, 1400 patients aged 13 to 39 years to either standard therapy or intensive treatment. After 6.5 years the standard therapy group achieved an HbA1c of 9.1% and the intensive group 7.4%. This resulted in a decreased relative risk of retinopathy by 76%, albuminuria by 54%, peripheral neuropathy by 60% and autonomic neuropathy by 53%. Members noted that a follow up trial, The Epidemiology of Diabetes Interventions and Complications study (EDIC) (Diabetes Care 1999;22:99-111), showed despite the convergence of the HbA1c levels within one year of the termination of DCCT, the vascular benefits persisted for at least another 10 years, suggesting that the benefits were not simply due to glycaemic differences during the trial.

- 8.6 The Committee considered a retrospective study of the management of patients with type 1 diabetes treated with insulin pump therapy in the Waikato (Reda et al NZ Med J 2007;120:U2401), which audited 105 patients, of whom 27 were adolescents. This was a before and after trial of patients who had previously used a Multiple Daily Injection (MDI) insulin regimen and were commenced on Continuous Subcutaneous Insulin Infusion (CSII) therapy. The average HbA1c reduced from 9.1% to 8.1% at three and six months; however the difference was not sustained at two or three years. The Committee considered that this may suggest the benefits in HbA1c were at least partially due to the intensive education required before CSII therapy was started. Members noted that the observed incidence of severe hypoglycaemia had reduced from 0.75 per year to 0.05 per year.
- 8.7 The Committee noted that the study conducted by Doyle et al (Diabetes Care 2004, 27:1554-8), using a modern insulin MDI regimen as the comparator, was the only identified randomised controlled trial (RCT) available for CSII therapy in paediatric patients. The CSII arm received 135 minutes of education while the MDI with glargine arm had 45 minutes of education. After 16 weeks, the CSII group had a reduction in HbA1c from 8.1% to 7.2% and the MDI group recorded no change in HbA1c at 8.2%. The number of episodes of diabetic ketoacidosis (DKA) and severe hypoglycaemic events were too low to show significant differences between the groups. There was no recorded difference in quality of life scores (QOL) between the two groups, although the study reported a strong selection preference for the ongoing or initiating use of CSII in each group. Members noted the potential for bias in the study from patients on CSII having greater patient education input.
- 8.8 The Committee noted that in unselected patient groups, as in the Bolli trial (Diabetes Care 2009;32:1170-6) there was no benefit in using insulin pumps compared with MDI. The Committee considered that the differential benefits of CSII were often difficult to assess as patients were offered more intensive education as part of the initiation process. The Committee noted the study by Thomas et al (Diabetes Medicine 2007;24:778-783) indicated that hypoglycaemic events could be significantly reduced by education alone (but at the expense of a higher HbA1c) when compared with CSII and MDI.
- 8.9 The Committee noted that the strength and quality of the evidence was weak, with no RCTs lasting longer than 24 weeks. The Committee noted that the majority of the clinical trials compared CSII with older insulin regimens (i.e. not long-acting), which were not directly comparable to modern diabetes care. Many trials were before/after in design, which the Committee considered could introduce significant bias in the form of intensive

education; where it is unclear how much of the benefit was due to the insulin pumps and how much was due to patient education.

- 8.10 The Committee noted the considerations and recommendations of the Diabetes Subcommittee on insulin pumps of March 2011, including the Subcommittee recommending the listing of insulin pumps and consumables for patients who meet the entry criteria with a high priority.
- 8.11 The Committee considered that the health benefits of CSII over MDI are difficult to prove. It noted that meta-analysis of RCTs quantifies only a small effect of CSII on HbA1c reduction in adults (Misso et al Cochrane Database of Systematic Reviews 2010, Issue 1) and children (Pankowska et al Paediatric Diabetes 2009;10:52-8); only one RCT lasting 16 weeks (Doyle et al Diabetes Care 2004,27:1554-8) showed a reduction of HbA1c in children/young people. No trials showed a clear benefit in the incidence of severe hypoglycaemia. The Committee noted that possible lifestyle benefits were highlighted by the responses to the PHARMAC request for information on insulin pumps (December 2010), which suggested a strong patient preference from those people using pumps; but that quality of life scores did not differ substantially between CSII and MDI groups in the studies.
- 8.12 The Committee considered that insulin pumps may provide a benefit for blood glucose control as they offer a programmable basal rate of insulin delivery. The Committee noted that this function would be particularly useful for patients who suffer nocturnal hypoglycaemia as the pump could be set to deliver a lower basal rate at predetermined times. Members noted that insulin pumps appear to reduce overall insulin usage, which results in less weight gain. The Committee noted that there may be lifestyle benefits for use in children, and pumps may benefit patients with gastroparesis, cystic fibrosis or other co-morbidities.
- 8.13 The Committee noted that cannula occlusion was a risk with insulin pumps and if undetected could lead to hyperglycaemia and DKA, but that this appeared to be less of a problem with the new pumps.
- 8.14 The Committee considered that patients should undertake an appropriate trial on MDI, including long acting insulin (currently insulin glargine is the only funded long acting preparation listed in the Pharmaceutical Schedule), prior to consideration for funded insulin pumps. The Committee noted that it was important to identify those patients with poor glycaemic control despite good adherence using a suitable insulin MDI regimen (that is, patients who suffer unpredictable and significant variability in blood glucose including significant hypoglycaemia affecting their ability to reduce HbA1c), as opposed to patients who did not adhere fully with treatment who could otherwise achieve good glycaemic control. The Committee considered that patients should receive education in carbohydrate counts and potentially a psychological assessment prior to consideration of an insulin pump.
- 8.15 The Committee noted that initiating a patient on an insulin pump required significant clinical involvement and work time. Members considered that DHBs may not have capacity for this and that it may be appropriate for DHBs without a diabetes multi-disciplinary team to work with a larger regional DHB for pump initiation. The Committee noted that it would be necessary to identify highly motivated patients and/or families who could meet the educative and ongoing monitoring requirements in order to use the pump

effectively. The Committee noted that appropriate education was required in order to ensure the optimal benefit for pump users.

- 8.16 The Committee **recommended** that insulin pumps should be funded using eligibility criteria to target those patient groups identified where the most benefit could be derived. Members **recommended** that the Diabetes Subcommittee should develop appropriate entry criteria and that stopping criteria should also exist in the event that clinical benefits are not maintained.
- 8.17 The Committee noted that the patient groups who would most benefit from insulin pump therapy were people with type 1 diabetes mellitus who: (i) cannot attain defined target HbA1c levels and who have frequent, severe and disabling hypoglycaemia; (ii) suffer nocturnal hypoglycaemia; (iii) are children less than 12 years of age in whom MDI is impractical or inappropriate; (iv) suffer from gastroparesis; (v) young patients with type 1 diabetes with early complications such as retinopathy. The Committee noted that some benefit could exist for teenage patients with type 1 diabetes, however there was little evidence to suggest a benefit of using insulin pumps in pregnant women with type 1 diabetes.
- 8.18 The Committee noted that there is an unmet need in the selected patient groups. In addition, while there is a lower overall incidence of type 1 diabetes in Māori and Pacific Island people, Māori and Pacific people who have type 1 diabetes have higher rates of microalbuminuria and suffer renal failure at an earlier age than non-Māori non-Pacific patients. The Committee considered that Māori and Pacific people with type 1 diabetes would be less able to self fund insulin pumps.
- 8.19 The Committee noted that the CUA performed by PHARMAC assumed a 0.7% reduction in HbA1c in calculating the proposed benefit of using CSII in comparison to MDI therapy. The Committee noted that this was an overestimate, as the Cochrane review of RCTs (Misso et al Cochrane Database of Systematic Reviews 2010, Issue 1) suggested that a reduction of HbA1c by CSII was 0.3% or less. Members considered that a reduction in HbA1c of 0.5% would be a clinically significant reduction, and that this would also be a reasonable assumption to use in the base case modelling scenarios. Members also considered that it would be appropriate to vary the HbA1c reductions in the model to a plausible range of 0.3% and 0.7%, which encompasses the uncertainties between the contrasting internal and external validities of the RCT (pessimistic 0.3%) and combined RCT/cohort study (optimistic 0.7%) estimates.
- 8.20 The Committee noted that there was a correlation between the stability of glycaemic control – maintaining smaller troughs and peaks in glucose levels – and microvascular complications. Members noted that HbA1c levels did not always identify patients with a wide variability in blood glucose levels, and considered that access criteria should allow for this. Members noted that it would be desirable to include this parameter in the CUA, but that due to uncertainty over its existence and magnitude, this might not yet be technically feasible.