PTAC meeting held 2 & 3 August 2012

(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 generally published.
- that any part of the minutes relating to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML) will be released, in a complete publication with the original Hospital Pharmaceuticals Subcommittee minutes and final recommendations made by PTAC, once PTAC have reviewed each therapeutic group.

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   Subcommittee Minutes

1.1   The Committee reviewed the Subcommittee Minutes detailed below and recommended that in future, where a subcommittee has made a recommendation, the relevant previous PTAC minutes must be available for the Committee to refer to.

1.2   Analgesic Subcommittee – 24 April 2012

    1.2.1   The Committee noted and accepted the record of the meeting in relation to items 1-5.

    1.2.2   The Committee noted that the remainder of the record related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML at its own meeting.

1.3   Anti-Infective Subcommittee – 31 May 2012

    1.3.1   The Committee noted and accepted the record of the meeting.

1.4   Cardiovascular Subcommittee – 7 June 2012

    1.4.1   The Committee noted and accepted the record of the meeting in relation to items 1-4.

    1.4.2   The Committee noted item 5, where the Subcommittee had reviewed dronedarone for atrial fibrillation and recommended that this be brought to PTAC for review.

    1.4.3   The Committee noted item 6, where the Subcommittee had reviewed ticagrelor for acute coronary syndromes. The Committee noted that ticagrelor was to be discussed at this meeting.

    1.4.4   The Committee noted item 7, where the Subcommittee had reviewed ivabradine for inappropriate sinus tachycardia and recommended that this be reviewed by PTAC once its registration had been approved.

1.5   Dermatology Subcommittee – 15 May 2012

    1.5.1   The Committee noted and accepted the record of the meeting in relation to items 1-4.

    1.5.2   The Committee noted that the remainder of the record related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML at its own meeting.

1.6   Diabetes Subcommittee – 20 April 2012

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1.6.1 The Committee noted and accepted the record of the meeting in relation to items 1-3.

1.6.2 The Committee noted item 4 related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML as part of a separate agenda item at this meeting.

1.6.3 The Committee noted items 5 – 7, where the Subcommittee had reviewed incretin therapies, linagliptin and liraglutide. The Committee noted that linagliptin and liraglutide were both being discussed at this meeting.

1.7 Gastrointestinal Subcommittee – 13 April 2012

1.7.1 The Committee noted and accepted the record of the meeting in relation to items 1 – 2.

1.7.2 The Committee noted in item 3, therapeutic group review, the Special Authority criteria which had been recommended for children for mesalazine sachets and dispersible tablet forms of omeprazole or esomeprazole were different. The Committee considered that both should be consistent therefore recommended that the criteria for mesalazine be amended to replace 'a patient under the age of 16' with 'child'.

1.7.3 The Committee noted points 3.19 – 3.20 in relation to rescue therapy for adalimumab and resolved that once PHARMAC staff had completed the analysis of this therapy, that this should be submitted to PTAC for review.

1.7.4 The Committee noted point 3.21, the recommendation for funding magnesium tablets, however, did not agree with the proposed Special Authority criteria. The Committee considered it would prefer initial applications from a relevant medical practitioner and that it should specify the extent of deficiency. The Committee recommended that, if a supplier was obtained for the New Zealand market, an application should be reviewed by PTAC.

1.7.5 The Committee noted item 4 related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML as part of a separate agenda item at this meeting. However, the Committee considered that the proposed Special Authority criteria for cisapride should it be funded, should be targeted to patients who have a severe gastrointestinal motility disorder and who are unresponsive to other treatments.

1.7.6 The Committee noted item 7, where the Subcommittee had reviewed sorafenib tosylate for the treatment of advanced inoperable hepatocellular carcinoma. The Committee did not support the Subcommittee's

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recommendation and reiterated its previous **recommendation** that the application be declined.

    1.7.7   The remainder of the minute was noted and accepted.

1.8   Pulmonary Arterial Hypertension Subcommittee – 6 December 2011

    1.8.1   The Committee noted and accepted the record of the meeting.

1.9   Respiratory Subcommittee – 16 February 2012

    1.9.1   The Committee noted and accepted the record of the meeting in relation to items 1-4.

    1.9.2   The Committee noted that the remainder of the record related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML as part of a separate agenda item at this meeting.

1.10   Hospital Pharmaceuticals Subcommittee – 3 July 2012

    1.10.1 The Committee noted the record of the meeting. The Committee noted that this related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML), and that PTAC would be formally reviewing these items for inclusion in a national PML as part of a separate agenda item at this meeting.

2   Rituximab for ANCA associated vasculitides and polyarteritis nodosa

Application

2.1   The Committee considered an application from the New Zealand Rheumatology Association (NZRA) for the funding of rituximab for patients with Anti-Neutrophil Cytoplasm Antibody (ANCA) associated vasculitides (AAV) and also for patients with non-hepatitis B related Polyarteritis Nodosa (PAN), where patients have a contraindication to cyclophosphamide or where their disease has failed to respond to conventional therapy.

Recommendation

2.2   The Committee **recommended** that rituximab should be funded, with a low priority, for patients with ANCA-AAV who have a contraindication to cyclophosphamide or where their disease has failed to respond to conventional therapy.

2.3   The Committee further **recommended** that PHARMAC request that the applicant provide criteria to define cyclophosphamide contraindication and patient intolerance or disease refractory to conventional treatments. Members also requested the applicants clarify the role of mycophenolate mofetil in treatment of ANCA-AAV.

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2.4   The Committee **recommended** that the application for rituximab for patients with non-hepatitis B related PAN be declined.

2.5   The Decision Criteria particularly relevant to these recommendations 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; (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.*

Discussion

2.6   The Committee noted that vasculitides associated with Anti-Neutrophil Cytoplasm Antibody (ANCA) comprise a group of systemic autoimmune diseases of unknown cause that effects small to medium sized blood vessels. Members noted that ANCA associated vasculitis (ANCA-AAV) include granulomatosis with polyangiitis (GPA) (formerly known as Wegener's granulomatosis (WG)), eosinophillic granulomatosis with polyangiitis (formerly known as Churg Strauss syndrome (CSS)) and microscopic polyangiitis (MPA)). Members noted that Polyarteritis Nodosa (PAN) affects medium sized blood vessels, and has many clinical findings in common with the ANCA-AAV.

2.7   The Committee considered that early diagnosis and treatment was important in preventing disease progression to end stage organ damage and lengthening life. Members noted that ANCA-AAV is associated with increased mortality with the main cause of death in the first year being infection, active vasculitis and renal failure, and thereafter, cardiovascular disease, malignancy and infection.

2.8   The Committee considered that PAN was extremely rare in New Zealand. The Committee noted that the 5 year prevalence of GPA and MPA in the Canterbury region was estimated to be 152 (112) and 58 (32) per million and noted that prevalence was approximately twice as high in people of European decent compared with Maori. The Committee considered that the applicant's estimate of approximately 40-50 patients per year accessing rituximab, if funded as requested, was reasonable.

2.9   The Committee noted that current standard treatment options, high dose glucocorticoids and immunosuppressants (cyclophosphamide, azathioprine, methotrexate or mycophenolate mofetil), had changed the course of ANCA-AAV from being an imminently life threatening condition to a chronic, relapsing and remitting, condition. However, members were unclear on the current usage and role of mycophenolate mofetil in this disease setting in NZ. Members noted that an observational study of 107 patients found that approximately 50% of treated patients experience one or more relapses by 5 years (Hogan et al 1996).

2.10   The Committee noted that the key evidence for the use of rituximab for inducing remission in patients with ANCA-AAV comprised of two prospective randomised controlled trials, RAVE (Stone et al 2010) and RITUXIVAS (Jones et al 2010). Members noted that neither of these trials were in patients refractory to conventional therapy or contraindicated to cyclophosphamide, which is the patient group the applicant has requested for funding.

2.11 The Committee noted that the RAVE trial was a multi-centre, randomized, double-blind, double-dummy, non-inferiority trial of rituximab (375 mg/m^2 per week for 4 weeks) compared with oral cyclophosphamide (2 mg/kg per day, up to a maximum of 6 months) for remission induction in 197 patients with severe ANCA-AAV (WG or MPA). Members noted that patients who achieved complete remission on cyclophosphamide were switched to azathioprine maintenance whereas patients on rituximab were switched to placebo. Members noted that 64% of patients in the rituximab group and 53% of patients in the cyclophosphamide group achieved complete remission without the use of prednisone by 6 months (a result that met the criterion for non-inferiority (p<0.001), however members considered that the margins for non-inferiority in this study were wide). Members noted that amongst patients with relapsing disease rituximab was more efficacious than cyclophosphamide for inducing remission of relapsing disease (34 of 51 patients (67%) compared with 21 of 50 patients (42%)). Members noted that there was no significant difference between treatment groups in severity of flares, quality of life or adverse events.

2.12 The Committee noted that long term data from the RAVE trial (published in abstract only, Specks et al Clinical and Experimental Immunology, 164 (Suppl. 1), 50–67) demonstrated that at 18 months 36% of the rituximab treated patients and 31% of the cyclophosphamide treated patients were in remission off glucocorticoids (p=n.s.), there was no difference between treatment groups in the number flares, glucocorticoid use or adverse events.

2.13 The Committee noted that the RITUXIVAS trial was an open label, randomised, study in 44 patients with newly diagnosed ANCA-AAV with renal involvement. Members noted that prior to enrolment patients were permitted to have had plasma exchange and prior treatment with methylprednisone. Members noted patients were randomised (3:1) to a standard glucocorticoid regimen plus either rituximab (375mg/m^2 per week) for 4 weeks with 2 IV cyclophosphamide pulses (with first and third rituximab dosing) (n=33, rituximab group), or IV cyclophosphamide for 3 to 6 months followed by azathioprine maintenance (n=11, control group). Members noted that there was no difference in the primary endpoint of sustained remission rates at 12 months (76% in the rituximab group vs. 82% in the control group), and no difference in the secondary endpoints of adverse event rates, quality of life or renal function improvement.

2.14 The Committee also reviewed evidence from a number of observational and single arm studies of rituximab in ANCA-AAV. Members noted that there was a paucity of evidence, limited to case reports, for the use of rituximab in patients with PAN.

2.15 Overall, The Committee considered that the evidence demonstrated that rituximab was as effective as cyclophosphamide in the treatment of ANCA-AAV. Members considered that rituximab may be better than cyclophosphamide in relapsing disease and may have some advantage in terms of being less immunosuppressive, and therefore potentially glucocorticoid sparing. Members noted that long term data was limited but encouraging. Members noted that the relapse rate in patients treated with rituximab was approximately 57% and considered it was likely that patients treated with rituximab induction would receive retreatment with rituximab on disease flare, likely every 6-18 months even though the applicant did not request rituximab for retreatment.

2.16 The Committee considered that given the increased cost of rituximab compared with cyclophosphamide it was reasonable to limit its funding to patients with severe ANCA-

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AAV contraindicated to cyclophosphamide or those refractory to, or intolerant of, conventional treatments and there was a need to clearly define this patient group in the funding criteria for rituximab. Members considered that the applicant should provide the criteria for cyclophosphamide intolerance.

2.17   The Committee noted that in May 2012, following a request for funding from a clinician, it had recommended that mycophenolate mofetil should be funded, with a high priority, for induction therapy in patients with vasculitis. However, members noted that correspondence with the applicant suggests that mycophenolate mofetil is not considered useful in this condition. The Committee requested that the applicant clarify the role of mycophenolate mofetil in vasculitis.

2.18   The Committee considered that there was insufficient evidence for the routine use of rituximab in PAN patients and considered that the NPPA pathway would be more suitable for these patients.

3   Ipilimumab for previously treated unresectable stage IIIc or IV melanoma

Application

3.1   The Committee considered an application from Bristol-Myers Squibb (NZ) limited for the listing of ipilimumab (Yervoy) on the Pharmaceutical Schedule for the treatment of patients with previously treated unresectable Stage IIIc or IV melanoma.

Recommendation

3.2   The Committee **recommended** that the application be declined. The Committee further **recommended** that the application be considered by the Cancer Treatments Subcommittee.

3.3   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 (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

3.4   The Committee noted that melanoma was very frequent in NZ with 2,256 new diagnoses and 317 deaths in 2008. Members noted that melanoma presents with a wide spectrum of clinical behaviour in patients ranging from presentation to death in a very short time frame (weeks) to indolent disease spanning decades. Members considered that immune control of the disease was an important factor in its progression with immune modulators, such as interleukin-2 (IL-2) showing some efficacy, albeit with significant side effects.

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3.5   The Committee considered that the current treatment options for advanced melanoma, including interferon alpha, IL-2, dacarbazine and temozolomide, were disappointing, and often associated with significant side effects, and there was a clear unmet health need for effective treatments in this setting.

3.6   The Committee noted that ipilimumab is a monoclonal antibody that blocks the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) on T-cells, this enhances T-cell activation, leading to indiscriminate activation of cell-mediated immune responses.

3.7   The Committee considered key evidence comprised a randomised, double blind, study in 676 HLA-A*0201 positive patients with unresectable Stage III or IV melanoma whose disease had progressed following prior treatment with chemotherapy or IL-2 (Hodi et al NEJM 2010). Members noted that patients were randomised 3:1:1 to receive ipilimumab (3 mg/kg) plus gp100 peptide, a tumour vaccine, (n=403), ipilimumab alone (n=137) or gp100 peptide alone (n=136) once every 3 weeks for 4 treatments. Members noted that patients could be retreated in the event of disease progression if they had demonstrated initial response or stable disease.

3.8   The Committee noted that the primary endpoint of the study was revised part way through the study from objective response rate to overall survival. Members noted that after a median follow-up of between 17.2-27.8 months there was a 3.7 month difference in median overall survival between the gp100 arm and the ipilimumab arms (6.4 months, 10 months, 10.1 months), however, members noted that the 95% confidence intervals overlapped, although the hazard ratio's for death reached statistical significance. Members noted that there was no difference in progression free survival between the three treatment groups.

3.9   The Committee considered that the Kaplan-Meier curves for survival appear to show an increased 'tail' of long term survivors for the ipilimumab treatment groups, however, members noted that the absolute percentage increase in survivors was small (around 10%) and was based on a small number of patients, n=42 at 3 years and n=8 at 4 years. Members considered that the combination of small numbers with long term follow-up and wide variation in natural history made it hard to estimate the true efficacy of ipilimumab in this study.

3.10   The Committee noted that ipilimumab treated patients in the Hodi study had significant autoimmune toxicities across various systems including the gastrointestinal tract, joints, skin liver and endocrine, with common symptoms (e.g. skin rash, diarrhoea, endocrine and hepatic events) occurring in 60% of patients treated with ipilimumab. Members noted that these toxicities were consistent with T-cell activated disease syndromes. Members considered that of most concern was GI toxicity which reached grade 3 or 4 in 5% of patients and was linked to 5 of 14 study deaths (via GI perforation).   Members further noted that patients with diarrhoea require early treatment with high doses of corticosteroids and may lead to hospitalisation and requirement for immunosuppressant treatments. Members also noted that study drug related mortality was 2%.

3.11   The Committee noted that Health related Quality of life (HRQoL) was measured in the Hodi study using the EORTC QLQ C-30 HRQoL questionnaire, members noted that overall there was no difference in quality of life score between the treatment groups.

3.12   The Committee also noted two other studies of ipilimumab (Prieto et al Clin Can Res 2012 and Robert et al NEJM 2011). Members noted that Prieto et al reported follow-up of 177 patients from 3 clinical trials in patients with metastatic melanoma who had received ipilimumab in combination with other treatments including IL-2 and gp100. Members noted that although results demonstrated 5 year overall survival rates of between 13- and 25% the absence of a control arm made it hard to draw any conclusion as to the relative efficacy of ipilimumab treatment.

3.13   The Committee noted that Robert et al was a randomised phase 3 study in 502 patients with previously untreated metastatic melanoma. Members noted that in this study patients were treated with a higher dose of ipilimumab (10 mg/kg) in combination with dacarbazine compared with dacarbazine alone. Members noted that ipilimumab treatment was associated with a 3.1 month improvement in overall survival (11.2 months vs. 9.1 months) and an approximate 8% absolute difference in 3 year overall survival from a population of 67 survivors. Members further noted that at 4 years the overall survival estimates for both arms was around 10%.

3.14   Overall, the Committee considered that there was strong evidence for a small increase (3 months) in median overall survival and weak evidence for an increase (about 10%) in 3-5 year survival in ipilimumab treated patients compared with control. However, members considered that ipilimumab was associated with significant immune related toxicities some of which may be long -term and some of which were fatal.

3.15   The Committee noted that ipilimumab was a very expensive treatment, and considered that the non-specific immune activation related toxicity of ipilimumab was too hazardous to justify the uncertain incremental benefits at the price offered.

4   TNF Inhibitors for Behçet's Disease

Application

4.1   The Committee considered an application from the New Zealand Rheumatology Association (NZRA) for the funding of TNF alpha inhibitors for the treatment of patients with Behçet's Disease who are refractory to conventional therapy.

Recommendation

4.2   The Committee **recommended** that a TNF inhibitor should be listed in the Pharmaceutical Schedule for patients with severe Behçet's Disease refractory to conventional therapy, with a medium priority. Members considered that although the evidence for efficacy of the individual TNF inhibitors was variable, it is likely they would all provide similar outcomes; therefore the Committee recommended that the funded TNF inhibitor should be the one associated with the lowest cost.

4.3   The Committee further **recommended** the application be referred to the Dermatology and Ophthalmology Subcommittees for advice on specific Special Authority criteria and if they had any preference for the specific TNF(s) to be funded.

4.4   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*

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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,

Discussion

4.5   The Committee noted that Behçet's Disease (BD) was a rare multi system, relapsing, chronic vasculitic disorder with prominent mucosal inflammation of unknown aetiology. Members noted that common manifestations included recurrent oral ulcers, ocular inflammation, genital ulcers, inflammatory arthritis and skin lesions. Members considered that the most serious manifestations included blindness, neurologic or gastrointestinal manifestations, venous thromboses, and arterial aneurysms which may be life threatening.

4.6   The Committee considered that BD significantly increases morbidity and mortality, with the leading cause of morbidity being eye involvement with potential threat of visual loss and 25% of patients becoming blind (Nessenblatt et al 1997) . Members noted that in a cohort study of 817 patients from a single centre in France overall mortality was 5% at 7.7 years (Saadoun et al 2010).

4.7   The Committee considered that BD was a relatively rare disease, with 16 known cases in NZ, however, members considered that this may be an underestimate of total cases in NZ but considered that the potential number of patients refractory to conventional therapy would be low.

4.8   The Committee considered that the impact of BD on the quality of life (QoL) of patients with serious manifestations was significant, especially for patients who are refractory to conventional therapy. Members noted that joint problems, neurological problems, pathergy reaction and bowel problems had the most impact on QoL, with the utility state of BD being similar to that of multiple sclerosis and active arthritis (Bernabé et al Rheumatology 2010). Members noted that loss of vision, neurological gastrointestinal and vascular manifestations of BD could cause permanent disability and associated increased societal and health care costs.

4.9   The Committee noted that the primary goal of BD treatment is symptom control, early suppression of inflammation and prevention of organ damage. Members noted that current treatment options include corticosteroids and/or immunosuppressants (e.g. methotrexate, azathioprine, cyclosporine and interferon alpha) and oral colchicine. Members noted that treatments are frequently used in combination in order to maximize efficacy while minimizing side effects.

4.10   The Committee considered that high quality evidence for treatment of BD was lacking with the most current treatments having been established primarily by extrapolation of their use and efficacy in other inflammatory conditions, such as rheumatoid arthritis. Members noted that whilst Behçet's disease had a range of clinical presentations the majority of evidence was limited to specific clinical presentations, mainly ocular involvement, and therefore it was difficult to extrapolate outcomes of these trials to other clinical manifestations of the disease, such as mucocutaneous manifestations.

4.11   The Committee considered that the evidence for use of TNF alpha inhibitors in Behçet's disease is of poor quality but of moderate strength comprising only one small randomized controlled trial (Melikoglu et al 2005 for etanercept) and several small

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observational studies and uncontrolled case-series. Members noted that the majority of evidence was from trials of infliximab. Members noted that there were no "head to head" studies comparing the various TNF alpha inhibitors but that overall there were more studies conducted with infliximab.

4.12 The Committee noted an analysis of published data for BD patients (Arida et al 2012) which concluded that the majority of patients treated with infliximab, etanercept or adalimumab showed improvements in mucocutaneous, ocular, gastrointestinal, and central nervous manifestations. Members considered that where efficacious, patients seemed to respond quickly to treatment between 1 and 3 months.

4.13 Members considered that although strong evidence is lacking, some agents appeared more useful than others for specific lesions. Members considered that for approximately 40% of patients, TNF alpha inhibitors may have long term sustained benefit but the majority of patients would require retreatment.

4.14 The Committee noted that TNF inhibitors were significantly more expensive than other conventional treatments for BD and considered that if funded the Special Authority criteria for TNFs should be strictly defined and that an audit of outcomes may be useful. Members considered that restrictions should be placed on the use of TNF alpha inhibitors such that funding was limited to patients with severe disease (e.g. patients with 2 or more relapses of posterior uveitis per year, low visual acuity due to chronic cystoid macular oedema, active CNS disease and/or selected patients with intestinal inflammation, or arthritic and mucocutaneous manifestations with significantly reduced quality of life) and refractory to conventional treatments.

5 Asenapine for Schizophrenia and Bipolar 1 Disorder

Application

5.1 The Committee considered a funding application from Lundbeck for asenapine (Saphris) in the treatment of schizophrenia and bipolar 1 disorder.

Recommendation

5.2 The Committee **recommended** that asenapine is funded for bipolar 1 disorder only if it is cost-neutral to aripiprazole and ziprasidone taking into account future generic pricing. The Committee also **recommended** that the application be referred to the Mental Health Subcommittee for advice on appropriate Special Authority criteria. The Committee **recommended** that the application for asenapine in schizophrenia be declined.

5.3 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 Maori and Pacific peoples (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule and (viii) The Government's priorities for health funding,*

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as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.

Discussion

Bipolar 1 disorder

5.4   The Committee noted that antipsychotic medications are not the mainstay of treating acute mania or mixed affective states and mood stabilisers such as lithium and sodium valproate are used for that. The Committee noted that monotherapy with an antipsychotic for acute mania is unusual and it would normally be an adjunct to mood stabilisers for maintenance treatment. However, the Committee noted that there are review articles presenting indirect comparisons of antipsychotics and mood stabilisers in acute mania which suggest that they could have a quicker onset of action and are potentially more effective. The Committee noted that the biggest difficulty in treating Bipolar 1 disorder is treating and preventing depression which is usually more severe, chronic and debilitating than mania.

5.5   The Committee noted the results over several studies on asenapine in Bipolar 1 disorder and considered that the evidence was of moderate strength and studies were of good quality. The Committee considered that the trials indicated that asenapine was inferior to olanzapine in clinical efficacy (McIntyre et al. J Affective Disord 2010a (122(1-2): 27-38 and McIntyre et al Bipolar Disorders 2009; 11: 815-826) but the differences were small. The Committee also noted that asenapine was associated with higher rates of extrapyramidal symptoms but lower rates of weight gain when compared to olanzapine (McIntyre et al. J Affective Disord 2010a (122(1-2): 27-38). The Committee noted that the supplier had undertaken some indirect analyses which indicated that asenapine had similar efficacy to quetiapine.

5.6   The Committee noted the results from Szegedi et al (Journal of Clinical Psychopharmacology 2012; 32(1): 1-10) where asenapine was compared to placebo in combination with mood stabilisers. The Committee noted the high placebo response which is likely due to the later onset of the effects of the mood stabilisers. The Committee noted that this study was relevant to New Zealand practice, noted the high dropout rates and had some concerns regarding the higher incidence of depression in patients who received asenapine.

5.7   The Committee considered that the risk-benefit for asenapine in bipolar 1 disorder remained positive and it was superior to monotherapy with mood stabilisers. The Committee however considered that there are currently many funded treatment alternatives. The Committee also had concerns regarding the compliance with this treatment given it is a sublingual wafer and requires twice daily treatment.

5.8   The Subcommittee considered that if asenapine is funded, patients already stable on other currently funded treatments would not be likely to switch. The Committee considered that it could be used in preference to ziprasidone (80% of ziprasidone use amongst new patients) but not aripiprazole (20% of aripiprazole use amongst new patients) in new patients. The Committee considered that it would not be used in preference to the more established treatments like olanzapine unless there is a concern regarding weight gain or lack of efficacy. The Committee considered that asenapine would likely be marketed as a mood stabiliser.

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5.9   The Committee noted that in bipolar disorder, asenapine would benefit those who have trialled and failed two other agents including risperidone, quetiapine or olanzapine. The Committee noted also there is likely to be dose-creep with this treatment as this is happening overseas.

Schizophrenia

5.10   The Committee noted evidence for asenapine in schizophrenia and considered that it was of weak strength and of moderate quality. The Committee considered that the evidence indicated that asenapine was not more effective than or only marginally more effective than placebo in the short-term trials for acute exacerbation of schizophrenia (clinical trial report summary (CTR) 041021 and CTR 041022).

5.11   The Committee noted that the Potkin et al study (J Clin Psych 2007 Oct; 68(10):1492-500) was the only one where asenapine showed clear benefit over placebo but there was a high number of dropouts and it had relatively low patient numbers. The Committee however noted that this was a common challenge in trials involving patients with acute psychosis and this was a relatively well-designed study. The Committee noted that asenapine, risperidone and placebo resulted in -15.9, -10.9 and -5.3 reduction in the PANSS (Positive and Negative Syndrome Scale) respectively. The Committee noted that compared with placebo, improvements on Clinical Global Impressions-Severity of Illness (CGI-S) and PANSS positive subscale scores were significantly greater with both asenapine ($p < .01$ and $p = .01$) and risperidone ($p < .005$ and $p < .05$). The Committee noted that the incidence of extrapyramidal symptoms (EPS) was similar for all three treatment arms but there was more weight gain with risperidone when compared to asenapine or placebo.

5.12   The Committee noted the results from the Schoemaker et al study (Pharmacopsychiatry 2010; 43: 138-146) which showed that there was a greater proportion of patients on olanzapine (57%) who completed the trial when compared to asenapine (38%). The Committee noted that the main reasons for discontinuation were withdrawal of consent (asenapine 22% versus olanzapine 16%), insufficient response (asenapine 25% versus olanzapine 14%) and adverse events (asenapine 6% versus olanzapine 7%). The Committee noted that there were more extrapyramidal side effects with asenapine when compared to olanzapine but olanzapine was associated with a higher rate of weight gain. The Committee noted that at all time points, clinical efficacy was superior with olanzapine when compared to asenapine.

5.13   The Committee noted that the European Medicines Agency considered that there was insufficient evidence to support the use of asenapine in schizophrenia and the FDA shared similar concerns and it also debated restricting the dosing for schizophrenia to 5mg twice daily.

6   Erythropoietin for Myelodysplasia

Application

6.1   The Committee reviewed a funding application from three clinicians on behalf of the Haematology Society of Australia and New Zealand (HSANZ) for erythropoietin (EPO) in patients with refractory anaemia associated with myelodysplasia (MDS).

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Recommendation

6.2   The Committee recommended that erythropoietin (EPO) is funded for patients with refractory anaemia associated with myelodysplasia (MDS) with low priority subject to Special Authority criteria which will be determined by PTAC after further analysis by PHARMAC staff.

6.3   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.*

Discussion

6.4   The Committee noted that this application was requested by PHARMAC staff after the Cancer Treatments Subcommittee noted that PHARMAC had received a number of Hospital Exceptional Circumstances (HEC) applications for EPO in patients with refractory anaemia associated with MDS.

6.5   The Committee noted that the incidence rates of MDS in New Zealand range from 2.8-9.6 per 100,000 (Irwin et al. Intern Med J 2011; 41(5): 399-407 and Smartt 2009, Horizon Scanning Report, Health Services Assessment Collaboration, Christchurch). The Committee also noted that the risk of disease increases with age and approximately 80% of patients are aged >60 years at diagnosis (Irwin et al. Intern Med J 2011; 41(5): 399-407). The Committee noted that 77% of New Zealand patients are classified as (International Prognostic Scoring System) IPSS low/intermediate 1 (Irwin et al. Intern Med J 2011; 41(5): 399-407).

6.6   The Committee noted that current treatment in New Zealand for MDS is supportive treatment with a small number of younger patients receiving allogeneic stem cell transplants. The Committee noted that azacitidine is a treatment option and is not currently funded. The Committee noted that it has previously been reviewed by PTAC and CaTSoP and received a recommendation for funding with a low priority for patients with intermediate-2 or high risk MDS, chronic myelomonocytic leukaemia or MDS related acute myeloid leukaemia. The Committee noted also that cyclosporin and lenalidomide are treatment option in some patients, although lenalidomide is not funded in New Zealand.

6.7   The Committee noted that Irwin et al (Irwin et al. Intern Med J 2011; 41(5): 399-407) reported in their cohort of 70 patients:

- 80% (56) received a blood transfusion at a mean rate of 4.3 units red blood cells (RBC) per month;

- 67% of these patients were classified with low/intermediate 1 MDS;

- 76% had ferritin levels recorded with a mean of 555mcg/L at diagnosis rising to 2963 mcg/L with more recent levels;

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- 2 out of the 56 patients who received blood transfusions were treated with desferrioxamine and only one patient had clinical iron overload; and

- Only 3 patients received a stem cell transplant.

6.8   The Committee noted that the National Comprehensive Cancer Network (NCCN) guidelines consider red blood cell transfusion as the standard of care for symptomatic anaemic patients and further management with EPO, G-CSF and/or lenalidomide is based on serum EPO levels, the number of ring sideroblasts and karyotyping. The Committee also noted that the American Society of Haematology (ASH) and American Society of Clinical Oncology (ASCO) recommend EPO to decrease the need for transfusion in patients with lower risk MDS (Rizzo et al. Blood 2010; 116: 4045-59).

6.9   The Committee noted that in 2000, an international working group developed a uniform set of guidelines for endpoints in future clinical trials in MDS including disease remission/ progression and the Committee noted that alleviation of disease-related complications and improved quality of life (QOL) were considered important goals of therapy (Cheson et al. Blood 2000; 96: 3671-4 and updated Cheson et al. Blood 2006; 108: 419-25).

6.10   The Committee considered that the evidence for EPO in MDS was of weak strength and low quality. The Committee considered that a few small randomised controlled trials showed a modest long term efficacy of the treatment. The Committee noted the results from a few meta-analyses (Moyo et al. Ann Hematol 2008; 87: 527-36, Mundle et al. Cancer 2009; 114(5): 706-15 and Ross et al. The Oncologist 2007; 12: 1264-73) and considered that they were of low quality and consisting mainly of observational cohort studies. The Committee considered that the meta-analysis by Mundle et al (Cancer 2009; 114(5): 706-15) was associated with potential bias where randomised controlled trials (RCTs) and observational studies were included without assessment or reporting of the quality of the studies and indirect comparisons were done between different treatment options without the use of appropriate methodology.

6.11   The Committee noted that the Moyo et al meta-analysis (Ann Hematol 2008; 87: 527-36) found that patients with lower staged MDS, lower serum EPO levels and receiving a fixed rather than a weight-based strategy were more likely to respond. The study also found that EPO alfa and darbepoietin resulted in similar erythroid response rates (57.6% versus 59.4% respectively).

6.12   The Committee noted that the RCT by Greenberg et al (Blood 2009; 114(12): 2393-400) was an unblinded RCT in 110 patients with mainly low and intermediate risk MDS which found that at 4 months, 36% of the EPO group had an erythroid response versus 9.6% in the control group (p=0.002) and 29% versus 51% were still receiving blood transfusions. The Committee noted that 6 out of 27 initial non-responders (22%) responded with subsequent addition of G-CSF and 6 out of 12 (50%) responded with subsequent doubling of EPO (300U/kg/day). The Committee noted that overall, 46.6% of patients responded to this treatment strategy and those with serum EPO <200 or with refractory anaemia +/- ring sideroblasts were more likely to respond in univariate analysis. The Committee noted that overall survival and AML transformation were similar between treatment arms although increased survival was demonstrated for erythroid responders versus non-responders (median of 5.5 versus 2.3 years). The

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Committee noted that transient thrombocytopenia and hyperbilirubinaemia were reported more frequently in the EPO group.

6.13   The Committee noted the results from the Italian Cooperative Study Group for MDS (Brit J Haem 1998; 103: 1070-4) which involved 87 patients with low and intermediate risk MDS and found that at 8 weeks, 36.8% of the patients who received EPO had an erythroid response versus 10.8% of control patients.

6.14   The Committee noted the results from the unblinded RCT by Casadevall et al (Blood 2004; 104: 321-7) which involved 60 patients with mainly low and intermediate risk MDS and serum EPO <500. The Committee noted that at 12 weeks, 42% of those who received EPO + G-CSF had an erythroid response versus none in the control patients. Two patients who responded had an increase in haemoglobin to at least 11.5g/dL and a further five became transfusion-independent. The Committee noted the results from Thompson et al (Blood 2000; 95: 1175-9) which was a double blind RCT in 66 patients with mainly low and intermediate risk, transfusion-dependent MDS. The Committee noted that although haemoglobin responses were marginally higher in the EPO group, only 4 out of 45 patients (9%) had a major erythroid response versus 1 out of 21 (5%) in the placebo group. The Committee noted that there was no difference in transfusion rates overall, although this was reduced in the subgroup with initial serum EPO levels <500 (60% versus 95%, p=0.007). The Committee noted that 3 EPO patients developed thrombocytopenia on treatment and 1 patient had a stroke.

6.15   The Committee noted that previous safety signals have indicated that EPO products do have the potential to potentiate tumour promotion and thromboembolic events but to date, no study has reported reduced survival in patients with MDS treated with EPO.

6.16   The Committee considered that most of the studies did not find that EPO resulted in an improvement in the quality of life for patients treated with EPO compared with blood transfusions. The Committee also considered that none of the RCTs reported overall survival benefit s or AML transformation benefits from treatment with EPO. The Committee considered that the main benefit from EPO in this indication would be avoiding blood transfusions.

6.17   The Committee considered that darbopoetin was found to have the same or similar therapeutic effect as erythropoietin EPO alfa in the Moyo meta-analysis (Moyo et al. Ann ematol 2008; 87: 527-36) but noted that this study was subject to bias. The Committee noted that ASH and ASCO consider EPO and darbopoietin equivalent with respect to effectiveness and safety and although this is mainly in relationship to chemotherapy induced anaemia, the Committee considered that it would be appropriate to consider them equivalent in this indication.

6.18   The Committee considered that it would be appropriate to estimate patient numbers based on the Irwin et al study (Irwin et al. Intern Med J 2011; 41(5): 399-407) because the dataset included access to all private and public bone marrow fundings in the region so it is likely to be more accurate. The Committee considered that it would be appropriate to estimate response rates (~36%) based on the RCTs results. The Committee considered that there is no evidence that failing EPO therapy changes the number of blood transfusions a patient would require. The Committee considered that EPO would be used in combination with G-CSF and there appears to be a modest

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gain when G-CSF is added to EPO in non-responders although the evidence for this is of low strength and quality.

6.19   The Committee considered that blood transfusions are a limited resource and that the cost of a unit of blood, as well as the cost of administration should be taken into account when estimating the cost-effectiveness in the economic analysis for this proposal. The Committee considered that based on the evidence, MDS patients with serum EPO levels <500 U/mL, with IPSS low/intermediate risk 1 disease, receiving concomitant iron administration and who have refractory anaemia with/without sideroblasts are most likely to benefit. The Committee considered that this was in line with the treatment algorithm proposed by the applicants.

6.20   The Committee noted that the incidence of MDS in Maori and Pacific peoples appears similar to other ethnic groups (Irwin et al. Intern Med J 2011; 41(5): 399-407).

7   Ticagrelor for Acute Coronary Syndrome

Application

7.1   The Committee reviewed a response from AstraZeneca to some issues raised by the Committee when it reviewed ticagrelor for the treatment of acute coronary syndrome (unstable angina, ST-elevation myocardial infarction (STEMI), non ST-elevation myocardial infarction (NSTEMI)) at its November 2011 meeting. The Committee also reviewed the minutes from the June 2012 Cardiovascular Subcommittee meeting where ticagrelor was discussed.

Recommendation

7.2   The Committee **recommended** that ticagrelor be funded on the Pharmaceutical Schedule for the treatment of patients with acute coronary syndromes with low priority subject to the following Special Authority criteria:

Initial application only from a relevant medical practitioner. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

   1   Any of the following:
        1.1   Patient has been diagnosed with ST-elevation myocardial infarction in the last 24 hours; or
        1.2 All of the following:
            1.2.1 Patient has been diagnosed with non ST-elevation acute coronary syndrome in the last 24 hours; and
            1.2.2 Patient has ischaemic chest pain of at least 20 minutes unresponsive to nitroglycerin; and
            1.2.3 Patient has an elevated troponin level (high sensitivity troponin T >50ng/L or troponin I above the reference range) with a documented rise and/or fall; and
            1.2.4 At least one of the following: age >60 years, previous coronary event, previous cerebrovascular event, diabetes mellitus, peripheral arterial disease, chronic renal dysfunction and/or dynamic ST elevation or depression >1mm on electrocardiogram; and

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2   Patient has not received fibrinolytic therapy in the last 24 hours or fibrinolysis is not planned; and

3   Any of the following:

   3.1   Patient has not received a loading dose of clopidogrel in the last 3 days or
   3.2   Patient is clopidogrel-allergic*

*Clopidogrel allergy is defined as a history of anaphylaxis, urticaria, generalised rash or asthma (in non-asthmatic patients) developing soon after clopidogrel is started and is considered unlikely to be caused by any other treatment.

7.3   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.*

Discussion

7.4   The Committee noted that it had previously reviewed ticagrelor for this indication at its November 2011 meeting where it recommended that the application be referred to the Cardiovascular Subcommittee for consideration, including for further advice on the extent that the outcomes of the PLATO and TRITON-TIMI 38 trials (for prasugrel hydrochloride) would be achieved in clinical practice, the identification of the patient groups that would receive the greatest clinical benefit from ticagrelor and the length of therapy that would result in the greatest clinical benefit being obtained. The Committee noted the minutes from the June 2012 Cardiovascular Subcommittee meeting relating to ticagrelor and also a response from the supplier on some of the issues PTAC highlighted at its November meeting.

7.5   The Committee considered that the response from the supplier in regards to the continued divergence of the efficacy curves for ticagrelor in the PLATO study (Wallentin L et al. N Engl J Med 2009; 361: 1045-57) was reasonable in that the results indicated a persistency and constancy of ticagrelor effect over the duration of the 12 months studied.

7.6   The Committee considered it was also reasonable to assume that the North American results where clopidogrel was observed to be superior to ticagrelor could be due to chance. The Committee considered that although it was possible that the higher aspirin dose used in North America could explain the difference in results, there is no biological basis to support this reasoning. Doubts remain as to the cause of the geographical differences particularly given that three countries (Poland, Hungary and Turkey) only enrolled 21% of patients yet yielded 46% of all endpoint events.

7.7   The Committee considered that the Cardiovascular Subcommittee comment (minutes 6.12, June 2012 meeting) that ticagrelor was more efficacious than clopidogrel for the primary endpoint in the Asia Pacific cohort may be inappropriate. Members suggested that it would be more appropriate to compare New Zealand to countries with similar medical practice to New Zealand such as USA (HR 1.27 n=1413), Canada (HR 1.17 n=401),, United Kingdom (HR 0.74 n=281), Australia (HR 2.45 n=83) and South Africa (HR 0.99 n=149) rather than Asia Pacific when considering the results of the PLATO study. The Committee noted that in Australia, which is the most comparable with NZ,

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ticagrelor was not found to be superior to clopidogrel (HR 2.45) although the confidence intervals remain wide. (Fiorentino. Clinical Efficacy Review, NDA 022433 Brilinta, ticagrelor. FDA, June 2010. Clinical efficacy review, page 94. Available at: http://www.fda.gov/downloads/Advisorycommittees/CommitteesMeetingMaterials/Drugs/Cardiovascularand%20RenalDrugsAdvisoryCommittee/UCM220192.pdf)

7.8   The Committee considered that the duration of treatment of 12 months requested by the supplier was debatable. The Committee considered that although this duration was chosen ahead of time and was chosen for the final analysis, randomisation only continued until a certain number of events was accumulated for the trial, at a mean of 298 days (supplier submission). The Committee noted that the supplier had the information to consider alternative treatment periods. The Committee noted that the supplier in their response to PTAC regarding the treatment period provided some information on the efficacy results at different time points. The Committee noted that the results for the primary end point (death from vascular causes, myocardial infarction (MI) or stroke) at 6 months for ticagrelor were 7.9% versus 9.2% for clopidogrel (an absolute risk reduction (ARR) of 1.3% and number-needed-to-treat (NNT) of 77) versus 9.8% versus 11.7% (ARR of 1.9% and NNT of 53) with 12 months treatment. The Committee considered that treatment with ticagrelor for 6 months would therefore be the most cost-effective as almost 70% of the ARR would have been obtained by this period and would be appropriate based on the evidence available.

7.9   The Committee also considered that the information provided by the supplier showed that 84% (729/864) of the ticagrelor events occurred in the first six months of the study. The Committee noted that evidence on switching patients to clopidogrel after 6 months treatment with ticagrelor is lacking; however, if most events are prevented early then 6 months treatment with ticagrelor followed by a switch to clopidogrel could be a way of accruing the benefit shown in the PLATO study while limiting the fiscal risk given the large price difference between clopidogrel ($0.18 per day) and ticagrelor ($4.85 per day).

7.10   The Committee agreed with the Subcommittee's comments that it was difficult to compare ticagrelor and prasugrel based on the two available clinical trials – PLATO and TRITON-TIMI 38, without a head-to-head trial. The Committee noted that the two studies recruited different populations. The Committee noted that the TRITON-TIMI 38 recruited younger patients, more men with fewer past histories of myocardial infarction (MI) and diabetes mellitus (DM). The Committee noted that in the PLATO trial, about 65% of the patients received a PCI and 10% coronary artery bypass grafting (CABG) compared to 99% and 1% in the TRITON-TIMI 38 trial.

7.11   The Committee noted two recent publications on the management and outcomes of patients with acute coronary syndromes in Australia and New Zealand (Alipranda-Costa B et al. MJA 2011; 195: 116-21 and Ellis C et al. NZMJ 2010; 123: 1319). The Committee considered that these publications indicate that the New Zealand population with ACS is older, with more women, more non-ST elevation ACS, higher rates of previous MIs and lower rates of DM with far less use of invasive strategies than in the PLATO trial. Alipranda-Costa et al reported that in a 2006/7 survey, within 6 months of the initial event 5.8% of patients had died. The Committee estimated that with the increase in clopidogrel use since then among other factors, the death rate would have reduced to 5.0% although this could still be an overestimation.

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7.12 The Committee noted that the Cardiovascular Subcommittee had considered that if there was a need to further tighten the Special Authority criteria to increase the cost-effectiveness or reduce the budget impact of funding ticagrelor, the criteria could be amended to exclude patients with unstable angina. The Committee considered however that it was difficult to distinguish the benefit between groups based on the results from PLATO trial and any restriction would be on fiscal grounds.

7.13 The Committee considered that the supplier's estimates of new ACS patients in New Zealand per year are likely an underestimate. The Committee noted that based on the publication by Ellis et al (Ellis C et al. NZMJ 2010; 123: 1319), there would be an estimated 20,000 patients with ACS in New Zealand per year. The Committee considered that the uptake of ticagrelor would be higher than the Subcommittee estimate, which is a third of new clopidogrel/prasugrel patients using ticagrelor. The Committee also considered that the supplier estimates of uptake were also likely to be an underestimate and that even existing patients already on clopidogrel would be switched to ticagrelor.

7.14 The Committee noted the recent American College of Cardiology Foundation/ American Heart Association (ACCF/AHA) 2012 focussed update of the guidelines for the management of patients with unstable angina/NSTEMI. The Committee noted that the guidelines did not recommend one of the three agents (clopidogrel, ticagrelor or prasugrel) as being preferred which is unusual for this publication. The Committee noted that these guidelines also recommended that the treatments be continued for up to 12 months rather than for 12 months.

7.15 The Committee noted the publication by Held et al (Journal of American College of Cardiology 2011 Feb 8;57 (6):672-84) and the results of the subgroup analysis in PLATO participants who underwent CABG. Unexpectedly mortality was halved in the group using ticagrelor compared to clopidogrel in the cohort that underwent CABG. This finding that 22/89 (25%) cardiovascular deaths occurred in only 6.8% of the total cohort is not fully explained by a plausible biological mechanism. The protocol for PLATO required that clopidogrel be withheld for 5 days before undergoing CABG while ticagrelor was only withheld for 1-3 days. The impact of this protocol difference is uncertain. Excessive bleeding is not considered to be the explanation for the mortality difference. Members raised concern of this unexplained findings impact on the overall study result.

7.16 Another subgroup finding inconsistent with an overall benefit for ticagrelor compared to clopidogrel was noted by the Committee. This was that in both STEMI and NSTEMI patients who underwent PCI within the first 10 hours, there was no mortality benefit for ticagrelor(Fiorentino. NDA 22-433 Brilinta, ticagrelor. FDA, July 2010. Efficacy review, page 18. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeet%20ingMaterials/ Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM221383.pdf.

7.17 The Committee considered that there is no clinical reason not to fund ticagrelor and the main issue is what the size of any clinical benefit is over current treatment, the length of treatment and the fiscal risk given the high price over clopidogrel and the large patient population. The Committee however noted that it had only one large Phase III clinical trial to base its recommendation on and it still had concerns about certain aspects of the PLATO study including geographical differences, unexplained

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CABG findings, PCI impact and overall applicability to the New Zealand setting. The Committee considered that the large proportion of patients in the clopidogrel arm (~60%) who received loading doses less than 600mg could have biased the results in favour of ticagrelor. The Committee noted also that compliance with ticagrelor would be lower in clinical practice because both clopidogrel and ticagrelor was subject to twice daily dosing in the PLATO trial although clopidogrel is a once-daily treatment. The Committee considered that this would reduce ticagrelor's efficacy advantage.

8   Progesterone for Menopause and Prevention of Preterm Labour

Application

8.1   The Committee considered an application from Pharmaco (NZ) Ltd for the funding of progesterone 100 mg capsules (Utrogestan) for adjunctive use with oestrogen in post-menopausal women with an intact uterus (hormone replacement therapy (HRT)). PHARMAC staff included an application to fund the vaginal use of progesterone capsules for the prevention of pre-term births in women with a short cervix and/or a history of pre-term births.

Recommendation

8.2   The Committee **recommended** that the application to list progesterone for hormone replacement therapy be declined. The Committee **recommended** that progesterone capsules be listed with a high priority for the prevention of pre-term births.

8.3   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.*

Discussion

Hormone Replacement therapy

8.4   The Committee noted that current practice for HRT of postmenopausal women is the addition of a progestogen for those women who have not had a hysterectomy to counter the substantial increased risk of endometrial cancer from unopposed oestrogen. The Committee noted that the only fully funded progestogens on the Pharmaceutical Schedule are the synthetic progestins and that this application was for the listing of a micronized progestagen chemically identical to natural progesterone.

8.5   The Committee considered the evidence found by Fahraeus et al. (Eur J Clin Invest 1983; 13(6):447-456) in relation to the risk of cardiovascular disease. The Committee noted that there was a significant decrease in total cholesterol and the HDL_2 fraction in the levonorgestrel group compared with those treated with progesterone and a reduction in the VLDL and LDL+HDL triglyceride fractions.   The Committee noted that

while these results were all tested as a difference from baseline it was not clear if they were significantly different from each other.

8.6   The Committee noted the results from the PEPI (Postmenopausal estrogen-progestin interventions) trial (JAMA 1995; 273(3):199. A three year, double blinded randomised control trial with 875 postmenopausal women enrolled and assigned to one of five arms: placebo; unopposed conjugated equine oestrogen (CEE); CEE plus medroxyprogesterone acetate (MPA) 2.5 mg continuous; CEE plus MPA 10 mg cyclic for 12 days per cycle; and CEE plus micronized progesterone (MP) 200 mg for 12 days per cycle. The Committee noted that all treatments significantly increased HDL levels, the CEE and MP arms increased HDL to a higher level than the MPA arms. All treatments decreased LDLC and total cholesterol and increased TGA levels with little difference between the groups.

8.7   The Committee noted that evidence for improved cardiovascular risk is made on the basis of weak evidence of the effects on biomarkers that are intermediate indicators and that no evidence was supplied that showed any clinically significant outcomes. The Committee noted that there is not an established link between the changes seen and the likelihood of improved outcomes in this group.

8.8   The Committee noted that, based on the E3N study (Fournier et al Breast Cancer Res Treat 2008 107(1):103-111), the supplier claims there is a reduced risk of breast cancer associated with micronized progesterone when compared with the synthetic progestogens. The Committee noted that this was a non-industry funded study within a cohort assessing risk factors for breast cancer in 98,995 women with 12 years follow-up. Follow-up in the postmenopausal subgroup of 80,377 women was for a mean of 8.1 postmenopausal years with HRT exposure data being collected from self-report questionnaires, and outcome data from self-report questionnaires, health insurance and death statistics. The Committee noted that in this study breast cancer occurred in 2.9% of the eligible postmenopausal cohort with the treatment relative risks as follows:

No treatment   relative risk 1.00 reference
Oestrogen alone   relative risk 1.29 (95% CI 1.02-1.65)
Oestrogen plus progesterone   relative risk 1.00 (95% CI 0.82-1.22)
Oestrogen plus dydrogesterone   relative risk 1.16 (95% CI 0.94-1.43)
Oestrogen plus other progestogens   relative risk 1.69 (95% CI 1.50-1.91)

8.9   The Committee noted that there was a statistically significant elevated risk in the progestogen group in the early years of treatment that was not present in the dydrogesterone and progesterone groups. There was a statistically significant trend (p=0.04) for increasing relative risk with increasing duration of exposure for progesterone. In all but the oestrogen only group, the risks disappeared after treatment had been stopped for two years.

8.10   The Committee considered that the supplier's claim of reduced risk is based on one cohort study and noted that there are no randomised head to head trials allowing for the comparison of overall effects on the range of potential adverse effects and benefits of different types of progestogens with micronised progesterone.

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Preterm Birth

8.11   At the request of PHARMAC staff, as a result of requests through the Named Patient Pharmaceutical Assessment (NPPA) scheme, the Committee considered the vaginal use of progesterone capsules in the prevention of preterm births in women with a short cervix and/or a history of pre-term births. The Committee noted that in Australia ~ 8% of all births are preterm (<37 weeks) and of those ~2.7% are pre 34 weeks which is the leading cause of increased rates of neonatal mortality and morbidity. The Committee noted that a short cervix (defined as <25 mm) and previous preterm births are two of the major identifiable risk factors for preterm births.

8.12   The Committee noted that Fonesca et al (N Eng J Med 2007; 357:462-469) measured the length of the cervix in 24,620 pregnant women and found that 413 of these women had a cervix of 15mm or less. Of these 413, 250 women were randomly assigned to receive vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks of gestation. The Committee noted that the rate of preterm births (<34 weeks) was significantly reduced in the progesterone group (19.2% vs. 34.4% in the placebo group), that there were no significant differences in the baseline characteristics of the two groups and no important adverse events or side effects in either group. The Committee noted there was no long term adverse event or outcome data.

8.13   The Committee considered a multicentre, randomised, double-blind, placebo controlled trial by Hassan et al (Ultrasound Obstet Gynecol 2011; 38:18-31) who screened 32,091 pregnant women and found 733 (2.3%) had a cervical length of 10-20 mm. Of these patients, 465 consented to be randomised to receive placebo or 8% vaginal progesterone gel daily. Hassan et al found a significant reduction of risk of a preterm birth (RR, 0.52; 95% CI, 0.31-0.91; p=0.02) in the progesterone group. Subgroup analysis showed in women without a history of preterm birth, vaginal progesterone gel administration was associated with a significant risk reduction of preterm birth before 33 weeks (RR, 0.5; 95% CI, 0.27-0.90; p=0.02) and a non-significant difference in those with a previous preterm birth, however there was no test for interaction. There was a significant reduction in neonatal respiratory distress syndrome (RR 0.42 95% CI 0.18-0.97). The Committee noted that adverse events were the same in the two groups, tended to be minor and local and that there was no long term adverse event or outcome data.

8.14   The Committee noted that a Cochrane review, updated in June 2012, assessed evidence from 11 randomised controlled trials and found a significant reduction in the relative risk of a preterm birth to women with a short cervix or those who present with threatened preterm labour. In multiple pregnancies there was no difference in pre-term birth however there was a significant reduction in antenatal tocolysis. The Committee noted the review found there was a reduction in low birth weight in infants born to women with a history of preterm birth (RR 0.64 95%CI 0.49-0.83), a reduction in neonatal sepsis in the short cervix subgroup (RR 0.28 95% CI 0.08-0.097) and reductions in low birth weight (RR 0.52 95% CI 0.28-0.98) and respiratory distress syndrome (RR 0.3 95% CI 0.11-0.83) in the threatened preterm labour subgroup.

8.15   The Committee noted the Guidelines in place for the use of progesterone for the prevention of preterm birth from the United States, Canada and New Zealand including a treatment protocol from Capital Coast DHB.

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8.16 In summary the Committee noted that while there was good quality evidence of a moderate strength for the vaginal use of progesterone for the prevention of preterm birth, the evidence for the use in HRT was moderate and of weak strength.

9 Protease Inhibitors for Hepatitis C

Telaprevir

Application

9.1 The Committee considered an application from Janssen-Cilag for the funding of telaprevir (Incivo) for the treatment of genotype 1 chronic hepatitis C.

Recommendation

9.2 The Committee **recommended** that telaprevir be listed on the Pharmaceutical Schedule with a high priority. Members noted that telaprevir is not the only protease inhibitor available for the treatment of genotype 1 chronic hepatitis C.

9.3 The Committee **recommended** that the Anti-Infective Subcommittee be asked to consider the application with a view to constructing Special Authority criteria for telaprevir.

9.4 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 (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

Discussion

9.5 The Committee noted that hepatitis C is relatively common in New Zealand with an estimated prevalence of 0.5-1.5% of the adult population and that genotype 1 makes up for approximately 54% of New Zealand's hepatitis C cohort. Members noted that the true prevalence of hepatitis C is unknown, but that it is presumed to be significantly higher than the diagnosed population.

9.6 The Committee noted that the current standard of care for patients with hepatitis C infection is pegylated interferon and ribavirin (PEG-RBV), which for genotype 1 is taken for 48 weeks. It is estimated that less than 50% of patients achieve a sustained virological response with currently funded treatments. Members noted that patients who are untreated or unsuccessfully treated have an increased risk of cirrhosis and hepatocellular carcinoma with the risk of progression to cirrhosis being 7% at 20 years and 20% at 40 years after acquiring infection. HCV related mortality is estimated to be 1% at 20 years and 4% at 40 years.

9.7 The Committee noted that the application contained good quality evidence in support of telaprevir. Members considered that the key evidence comprised of three phase III double blind placebo controlled RCTs examining telaprevir in conjunction with pegylated interferon and ribavirin:

- ADVANCE (Jacobson et al. N Engl J Med 2011; 364:2405-16), which recruited treatment-naive patients. Patients were randomised to 8 or 12 weeks of telaprevir or placebo, in addition to 24-48 weeks of PEG-RBV.

- ILLUMINATE (Sherman et al. N Engl J Med 2011; 365:1014-24), which compared 12 weeks of telaprevir in addition to either 24 or 48 weeks of PEG-RBV.

- REALISE (Zeuzem et al. N Engl J Med 2011; 364:2417-28), which included patients who had previously been treated with pegylated interferon and ribavirin. Patients were given 48 weeks of PEG-RBV, and were randomised to receive either 12 weeks or telaprevir, either from treatment commencement or after four weeks, or placebo.

9.8   The Committee noted that these studies demonstrated that telaprevir increases the rate of sustained virological response in both treatment-naïve and treatment-experienced patients.

9.9   The Committee noted that there were significant skin and haematological side effects with telaprevir.

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9.10   The Committee considered that it would be important to target access to telaprevir, given the high cost of this agent. Members noted that there are new initiatives being implemented to increase the diagnosis rates of people infected with hepatitis C, which could potentially have a substantial effect on the costs of hepatitis C treatments due to more people being diagnosed.

9.11   Members noted that IL28 screening can have some use in predicting response to PEG-RBV, and questioned whether this could be used as part of the access criteria for telaprevir.

9.12   The Committee considered that there should be consideration given to exit criteria so that over-treatment of both excellent and poor responders does not occur. Members also noted that, if telaprevir was funded, the Special Authority criteria for PEG-RBV would need to be amended to allow for re-treatment.

9.13   The Committee noted that due to the very high cost of treatment of end stage liver disease and transplantation and the poor associated QoL that the cost per QALY would be likely favourable with the protease inhibitors. Members noted that the increased access to protease inhibitors would increase the usage of PEG-RBV and this may lead to increased hospitalisations to treat side effect.

9.14   The Committee noted that there were differences between the two protease inhibitors (currently being considered for funding) in terms of different regimens side effects and costs, no direct comparisons studies between boceprevir and telaprevir have been conducted, and thus neither drug can be recommended over the other based on efficacy grounds. Members noted that the frequency of administration of the dosing regimens may have an impact on compliance.

Boceprevir

Application

9.15   The Committee considered an application from Victrelis, Merck Sharp & Dohme, for the   funding of boceprevir for the treatment of genotype 1 Hepatitis C

Recommendation

9.16   The Committee **recommended** that boceprevir be listed on the Pharmaceutical Schedule with a high priority. Members noted that boceprevir is not the only protease inhibitor available for the treatment of genotype 1 chronic hepatitis C.

9.17   The Committee **recommended** that the Anti-Infective Subcommittee be asked to consider the application with a view to constructing Special Authority criteria for boceprevir.

9.18   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*

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Discussion

9.19   The Committee noted that hepatitis C is relatively common in New Zealand with an estimated prevalence of 0.5-1.5% of the adult population and that genotype 1 makes up for approximately 54% of New Zealand's hepatitis C cohort. Members noted that the true prevalence of hepatitis C is unknown, but that it is presumed to be significantly higher than the diagnosed population.

9.20   The Committee noted that the current standard of care for patients with hepatitis C infection is pegylated interferon and ribavirin (PEG-RBV), which for genotype 1 is taken for 48 weeks. It is estimated that less than 50% of patients achieve a sustained virological response with currently funded treatments. Members noted that patients who are untreated or unsuccessfully treated have an increased risk of cirrhosis and hepatocellular carcinoma with the risk of progression to cirrhosis being 7% at 20 years and 20% at 40 years after acquiring infection. HCV related mortality is estimated to be 1% at 20 years and 4% at 40 years.

9.21   The Committee noted that the application contained good quality evidence in support of boceprevir. Members considered that the key evidence comprised of two phase 3 studies examining boceprevir, in conjunction with pegylated interferon and ribavirin:

   • RESPOND-2 study. (Bacon et al. N Engl J Med 2011; 364(13):1207-17) which considered boceprevir for previously treated chronic HCV genotype 1 infection. Patients were randomised to three groups, pegylated interferon alfa-2b and ribavirin were administered for 4 weeks (the lead-in period). Subsequently, group 1 (control group) received placebo plus pegylated interferon -ribavirin for 44 weeks; group 2 received boceprevir plus pegylated interferon -ribavirin for 32 weeks, and patients with a detectable HCV RNA level at week 8 received placebo plus pegylated interferon with ribavirin for an additional 12 weeks; and group 3 received boceprevir plus pegylated interferon with ribavirin for 44 weeks

   • SPRINT-2 trial. (Poordad F et al. N Engl J Med. 2011; 364 (13):1195-206.), which considered boceprevir for treatment naïve patients. In all three groups, pegylated interferon alfa-2b and ribavirin were administered for 4 weeks (the lead-in period). Subsequently, group 1 (the control group) received placebo plus pegylated interferon -ribavirin for 44 weeks; group 2 received boceprevir plus pegylated interferon -ribavirin for 24 weeks, and those with a detectable HCV RNA level between weeks 8 and 24 received placebo plus pegylated interferon -ribavirin for an additional 20 weeks; and group 3 received boceprevir plus pegylated interferon with ribavirin for 44 weeks.

9.22   The Committee noted that these studies demonstrated that boceprevir increases the rate of sustained virological response in both treatment-naïve and treatment-experienced patients. The Committee noted that boceprevir may be associated with a higher rate of anaemia as an adverse effect which might have cost implications (for example, the potential requirement of erythropoietin to treat anaemia).

9.23   The Committee considered that it would be important to target access to boceprevir, given the high cost of this agent. Members noted that there are new initiatives being implemented to increase the diagnosis rates of people infected with hepatitis C, which

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could potentially have a substantial effect on the costs of hepatitis C treatments due to more people being diagnosed.

9.24 Members noted that IL28 screening can have some use in predicting response to PEG-RBV, and questioned whether this could be used as part of the access criteria for boceprevir.

9.25 The Committee considered that there should be consideration given to exit criteria so that over-treatment of both excellent and poor responders does not occur. Members also noted that, if boceprevir was funded, the Special Authority criteria for PEG-RBV would need to be amended to allow for re-treatment.

9.26 The Committee noted that due to the very high cost of treatment of end stage liver disease and transplantation and the poor associated QoL, that the cost per QALY would be likely favourable with the protease inhibitors. Members noted that the increased access to protease inhibitors would increase the usage of PEG-RBV and this may lead to increased hospitalisations to treat side effect.

9.27 The Committee noted that there were differences between the two protease inhibitors (currently being considered for funding) in terms of different regimens, side effects and costs. No direct comparisons studies between boceprevir and telaprevir have been conducted, and thus neither drug can be recommended over the other based on efficacy grounds. Members noted that the frequency of administration of the dosing regimens may have an impact on compliance.

10 Liraglutide for Type 2 Diabetes

Application

10.1 The Committee considered an application from NovoNordisk for liraglutide (Victoza) for the treatment of type 2 diabetes.

Recommendation

10.2 The Committee **recommended** that 1.2 mg liraglutide be funded with a low priority and **recommended** that the Diabetes Subcommittee provide further definitions for targeting patients with occupational risk of hypoglycaemia prior to funding. The Committee suggested the following draft Special Authority criteria:

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

1. Either

    1.1. Patient is not achieving effective control of HbA1c on maximum tolerated doses of metformin for the previous 6 months and is unable to use insulin or sulphonylurea therapy due to occupational risk of hypoglycaemia; or

    1.2. Patient is not achieving effective control of HbA1c on a maximum tolerated dose of thiazolidinedione for the previous 6 months and metformin is contraindicated; and

2. Liraglutide will be used in combination with one or more oral treatments; and

3. Patient has a BMI of >35 kg/m2; and

4. It is anticipated that liraglutide will reduce HbA1c by at least 10 mmol/mol

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Renewal from any medical practitioner. Approvals valid for six months for applications meeting the following criteria:
1. Patient has achieved an HbA1c reduction of 10 mmol/mol from baseline; and
2. Patient has not gained weight from baseline

10.3   *The Decision Criteria particularly relevant to this recommendation are: 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; (iv) the clinical benefits and risks of pharmaceutical; (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

10.4   The Committee noted that liraglutide is a GLP-1 mimetic which is slowly absorbed following subcutaneous administration and has a unique mode of action in comparison to other funded pharmaceuticals for the treatment of hyperglycaemia associated with type 2 diabetes.

10.5   The Committee considered a meta-analysis comparing the effect of intensive against standard glucose lowering treatment on all-cause mortality, cardiovascular death and microvascular events in randomised controlled trials (Boussageon. BMJ 2011; 343:d41369). The analysis included 34,533 patients with type 2 diabetes with a mean HbA1c of 7.9% at baseline who were randomised to receive intensive or standard diabetes treatment. The mean duration of follow up was 5 years. The Committee noted that intensive treatment did not significantly affect all-cause mortality (risk ratio 1.04, 99% CI 0.91-1.19) or cardiovascular death (1.11, 0.86-1.43) and the mean HbA1c of the intensive group was 6.7% compared with 7.5% in the standard treatment arm. The Committee noted that the intensive treatment arm reported a more than a two fold increase in the risk of severe hypoglycaemia (2.33, 21.62 – 3.36, p<0.001). The Committee considered that this meta-analysis indicates that there may be limited benefits associated with intensive diabetes management and rates of hypoglycaemic events increase with treatment intensification.

10.6   The Committee considered the evidence provided in the application to be of moderate strength and good quality. The Committee considered the studies included in the LEAD clinical development programme which recruited more than 4,000 patients. The LEAD programme included seven studies comparing the effect of varying doses of liraglutide in monotherapy or in combination and rosiglitazone 4 mg (LEAD-1), glimepride 4 mg (LEAD-2), glimepride 8 mg (LEAD-3), placebo (LEAD-4), insulin glargine 24 iu/day (LEAD-5), exenatide 10 mcg twice daily (LEAD-6) and sitagliptin 100 mg once daily (Study NN2211-1860).

10.7   The Committee considered the LEAD-5 study (Russell-Jones et al. Diabetologia 2009;52: 2046-2055), which reported that liraglutide 1.8 mg daily reduced HbA1c by 0.24% (95%CI, -0.39 to -0.08; p=0.0015) more than insulin glargine 24 units daily. Both treatments were used in combination with titrated metformin and glimepride however the dose of glimepride was reduced from 4 mg to 2 mg if patients reported hypoglycaemia. The Committee noted that weight was reduced for patients in the

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liraglutide arm and increased for patients using glargine, with an end of study difference of 3.4 kg, and systolic blood pressure difference was 4.5 mmHg, both in favour of liraglutide after 26 weeks. The Committee noted that five patients in the liraglutide arm reported major hypoglycaemic events (2.2%) in the 26 weeks with none reported in the glargine or placebo arm. The Committee considered that this raises questions regarding amelioration of the benefits of liraglutide when used in combination with sulphonylurea's when compared with glargine.

10.8   The Committee considered a review of the LEAD programme (Davies et al. Diabetes, Obesity and Metabolism 2011; 13:207-220) which reported that liraglutide decreased HbA1c by up to 1.5% which was greater than for all comparators, except in LEAD-2 when it showed equivalence with glimepride 4 mg.

10.9   The Committee considered a meta-analysis of the LEAD trials (Henry et al. Endocrine Pract. 2011; 17:906-13) which assessed the efficacy of anti-hyperglycaemic therapies (liraglutide 1.8 mg dose only compared with glimepride, rosiglitazone, metformin, exenatide, sitagliptin and insulin glargine) and the influence of baseline HbA1c on outcomes. The authors reported that liraglutide produced the greatest HbA1c reduction in each band, ranging from 0.7% reduction in patients with HbA1c <7.5% to 1.8% reduction in patients with HbA1c >9%. The authors considered that insulin glargine was the next most effective treatment at reducing HbA1c, however the Committee considered that in practice, the dose of insulin can be titrated to achieve greater effect, whereas the dose of liraglutide is not to date approved for use above 1.8 mg daily.

10.10   The Committee considered a study (Nauck et al. BP Res Clin Endo and Met 2009; 23: 513-23) which looked at how incretin mimetics and di-peptidyl peptidase inhibitors (DPP-4s) fit into treatment algorithms for type 2 diabetes patients. The Committee noted that the study promotes the use of metformin uniformly as first line treatment as it promotes weight loss, doesn't cause hypoglycaemic events and reduces cardiovascular events however metformin is not tolerated in 10% of patients. The Committee considered that second line options include sulphonylureas (SUs), acarbose and thiazolidinediones.

10.11   The Committee considered that the benefits of incretin mimetics go beyond their effect on HbA1c reduction. The Committee considered that in clinical practice, appropriately titrated insulin doses are likely to produce a greater effect on HbA1c reduction than in the LEAD-5 study. The Committee noted that liraglutide is generally associated with low rates of hypoglycaemia compared with other therapies however, based on the evidence provided, it would be difficult to estimate the difference between the rate of hypoglycaemia events when comparing liraglutide with glargine. The Committee considered that the "real world" picture is likely to favour liraglutide however, due to a set dose (avoiding injection errors) and the fact that it only acts if there is glucose in the GI tract. The Committee considered that liraglutide has a positive effect on weight compared with insulin, and considered that the difference observed in the short term studies is likely to be greater over time. The Committee considered that the need to inject liraglutide is less acceptable to patients than taking a tablet.

10.12   The Committee considered that it is likely that liraglutide would be used in combination with one or more of the following oral agents: metformin, sulphonylureas and TZDs. The Committee considered that it is likely that treatment with liraglutide if tolerated would continue for between 3 to 5 years and may delay the need for some patients to

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begin insulin therapy. The Committee noted that there appears to be little difference in the clinical effect achieved by using 1.2 mg vs 1.8 mg liraglutide.

10.13 The Committee noted the high cost of liraglutide and considered that appropriate entry and exit criteria would be necessary. The Committee considered that patients who are likely to receive the greatest benefit from treatment with liraglutide are those with a BMI>35 kg/m2 due to the weight benefits, and patients who must avoid treatments which cause hypoglycaemia due to occupational risks, however the Committee noted that defining the latter group of patients could be difficult. The Committee considered that the Diabetes Subcommittee should provide further definitions for patients who are at occupational risk and that New Zealand Transport Authority and other licencing bodies could be consulted. The Committee considered that an adequate trial of tolerated first and second line oral agents would be appropriate, noting that this may include a trial of a DPP-4 agent should these be funded.

11   Linagliptin for Type 2 Diabetes

Application

11.1   The Committee reviewed a joint funding application from Boerhinger Ingelheim and Eli Lilly for linagliptin (Trajenta) for the treatment of type 2 diabetes.

Recommendation

11.2   The Committee **recommended** that linagliptin be funded with a low priority and **recommended** that this low priority recommendation be applied to other previously reviewed dipeptidyl peptidase-4 inhibitors vildagliptin and sitagliptin.

Initial application from any medical practitioner. Approvals valid for six months for applications meeting the following criteria:
1. Either:
   1.1. Patient is not achieving effective control of HbA1c despite treatment with maximum tolerated doses of metformin and sulphonylurea for at least 6 months; or
   1.2. Patient is not achieving target HbA1c despite treatment with maximum tolerated doses of sulphonylurea and metformin is contraindicated; or
   1.3. Patient is not achieving target HbA1c on maximum tolerated doses of metformin for the previous 6 months and is unable to use insulin or sulphonylurea therapy due to occupational risk;
2. It is anticipated that a reduction in HbA1c of 5 mmol/mol would achieve HbA1c target

Renewal from any medical practitioner. Approvals valid for six months for applications meeting the following criteria:
1. Patient has achieved an HbA1c reduction of at least 5 mmol/mol from baseline

11.3   *The Decision Criteria* particularly relevant to this recommendation are*: 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; (iv) the clinical benefits and risks of pharmaceutical; (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.*

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Discussion

11.4   The Committee considered a meta-analysis comparing the effect of intensive against standard glucose lowering treatment on all-cause mortality, cardiovascular death and microvascular events in randomised controlled trials (Boussageon. BMJ 2011; 343:d41369). The analysis included 34,533 patients with type 2 diabetes with a mean HbA1c of 7.9% at baseline who were randomised to receive intensive or standard diabetes treatment. The mean duration of follow up was 5 years. The Committee noted that intensive treatment did not significantly affect all-cause mortality (risk ratio 1.04, 99% CI 0.91-1.19) or cardiovascular death (1.11, 0.86-1.43) and the mean HbA1c of the intensive group was 6.7% compared with 7.5% in the standard treatment arm. The Committee noted that the intensive treatment arm reported a more than a two fold increase in the risk of severe hypoglycaemia (2.33, 21.62 – 3.36, p<0.001). The Committee considered that this meta-analysis indicates that there may be limited benefits associated with intensive diabetes management and rates of hypoglycaemic events increase with treatment intensification.

11.5   The Committee noted the Ministry of Health guidance on the management of type 2 diabetes released in 2011 which state that the target HbA1c is 50-55mmol/mol (6.8-7.2%) (however this can be individualised) and that any reduction in HbA1c is beneficial.

11.6   The Committee noted that linagliptin is a dipeptidyl peptidase-4 inhibitor (DPP-4) with the main point of difference compared with other DPP-4's previously reviewed is that it is not renally excreted.

11.7   The Committee considered a multicentre, randomised, double blind, placebo controlled study investigating the safety and efficacy of linagliptin as an add-on therapy to metformin in patients with type 2 diabetes (Taskinen et al. Diabetes Obes Metab. 2011 Jan;13(1):65-74). The primary outcome was the change from baseline in HbA1c after 24 weeks of treatment Linagliptin showed significant reductions vs. placebo in adjusted mean changes from baseline of HbA1c (-0.49 vs. 0.15%, p < 0.0001). The Committee noted that hypoglycaemia was rare, occurring in three patients (0.6%) treated with linagliptin and five patients (2.8%) in the placebo group and body weight did not significantly change in either group. The Committee noted that three trial protocols were provided in the application however the published studies for these could not be found.

11.8   The Committee considered two studies to provide a comparison between the efficacy and safety of linagliptin and sitagliptin and vildagliptin. The Committee also considered all previous minutes from DPP-4 reviews. The Committee considered a placebo controlled study (Charbonell et al. Diabetes Care 2006; 29: 2638-43) which evaluated the effect of add-on sitagliptin 100 mg to patients taking at least 1500 mg metformin daily. The Committee noted that the reduction in HbA1c at week 24 was -0.65% compared with the placebo group. The Committee noted that sitagliptin was associated with a slightly higher incidence of urinary tract infections, nasopharyngitis, arthralgia and back pain, however there was a lower incidence of hypoglycaemia compared with the placebo group.

11.9   The Committee considered a 52 week multicentre, randomised, double-blind active controlled study comparing the efficacy and safety of vildagliptin 50 mg twice daily and

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glicalazide 80 mg daily in combination in patients with type 2 diabetes who were inadequately controlled with metformin (1500 mg daily) alone. The authors reported the vildagliptin was non-inferior to gliclazide with a mean reduction from baseline HbA1c at 52 weeks of -0.81% (p=0.06) with vildagliptin and -0.85% (p=0.06) and there were fewer hypoglycaemic events in the vildagliptin group.

11.10 The Committee noted that only one recent study compares DPP-4s with insulin, and then only looks at efficacy not safety. The Committee noted that EASIE was a 6 month, multicentre, randomised open label trial which assessed the effect of insulin glargine vs sitagliptin in 515 insulin naive patients with type 2 diabetes (Aschner et al. Lancet 2012; 379: 2262-69). The primary objective was to show the superiority of insulin glargine over sitagliptin in reducing HbA1c from baseline. The Committee noted that the adjusted mean difference in HbA1c between groups was -0.59% in favour of glargine.

11.11 Overall, the Committee considered that vildagliptin, linagliptin, sitagliptin and saxagliptin have a similar modest effect to reduce HbA1c and appear to offer weight neutral benefits. The Committee considered that there are some differences in pharmacokinetic profiles between agents, with linagliptin exhibiting non-renal elimination and therefore no dose reduction is necessary in renal impairment.

11.12 The Committee considered that DPP-4s would be best used in patients needing to avoid hypoglycaemia for occupational safety reasons who are near target HbA1c, however noted that the effect on reducing HbA1c levels may be too weak to avoid the need for SU or insulin therapy. The Committee considered that DPP-4's be used after adequate trials of metformin and sulphonylureas and that entry and exit criteria should apply with patients required to demonstrate an HbA1c reduction from baseline.

11.13 The Committee considered that the Diabetes Subcommittee should provide further definitions for patients who are at occupational risk and that New Zealand Transport Authority and other licencing bodies could be consulted.

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