

## PTAC meeting held 13 & 14 August 2009

### (minutes for web publishing)

PTAC minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not necessarily a complete record of the PTAC meeting; only the relevant portions of the minutes relating to PTAC discussions about an application that contain a recommendation are published.

PTAC may:

- (a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- (b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- (c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA), in order to protect the privacy of natural persons (section 9(2)(a)).

---

## Contents

1	Clopidogrel for Stroke and Transient Ischaemic Attack (TIA), Acute Coronary Syndrome and Revascularisation, and Aspirin Intolerance .....	2
2	COX-2 Inhibitors for Severe Haemophilia Complicated by Arthropathy.....	5
3	Ambrisentan (Volibris) for Pulmonary Arterial Hypertension .....	6
4	Aliskiren (Rasilez) for Hypertension.....	7
5	Riluzole (Rilutek) for Amyotrophic Lateral Sclerosis.....	8
6	Thalidomide for the Treatment of Patients with Newly Diagnosed Multiple Myeloma ....	10
7	Lenalidomide for Relapsed/Refractory Multiple Myeloma .....	13
8	Bortezomib for Multiple Myeloma.....	15
9	Sorafenib for the Treatment of Hepatocellular Carcinoma .....	17
10	Budesonide (Entocort CIR) for Crohn's Disease, Microscopic Colitis and Graft versus Host Disease .....	19
11	Insulin Glargine (Lantus) for Treatment of Diabetes Mellitus.....	22
12	Access to Treatments for Multiple Sclerosis .....	23

# 1 Clopidogrel for Stroke and Transient Ischaemic Attack (TIA), Acute Coronary Syndrome and Revascularisation, and Aspirin Intolerance.

## Application

- 1.1 The Committee considered a memorandum from PHARMAC staff reviewing the current clopidogrel Special Authority criteria.

## Recommendation

- 1.2 The Committee **recommended** that clopidogrel monotherapy be listed as an alternative to aspirin and dipyridamole combination therapy in stroke and transient ischaemic attack (TIA) patients if it is cost-neutral.
- 1.3 The Committee **recommended** that aspirin and clopidogrel combination therapy should be subsidised for 30 days in patients with a high risk TIA within the last seven days (as defined by an ABCD2 score of four or more), or with two TIAs in the last seven days, with a low to medium priority.
- 1.4 The Committee **recommended** that the treatment period of clopidogrel for patients with acute coronary syndrome or a revascularisation procedure (including the insertion of a stent) should be extended to 12 months with a low priority.
- 1.5 The Committee **recommended** that widening access to clopidogrel to include patients who are aspirin intolerant due to GI bleeding be declined.
- 1.6 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (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

### 1.7 Stroke and TIA

- 1.8 The Committee noted that currently funded antiplatelet treatments for patients following a stroke or TIA are aspirin monotherapy, dipyridamole monotherapy, aspirin and dipyridamole combination therapy, and clopidogrel (if the patient is aspirin allergic).
- 1.9 The Committee considered whether clopidogrel monotherapy could be used as an alternative to aspirin and dipyridamole combination therapy. The Committee noted that the ProFESS trial (Diener et al, 2008: Lancet Neurol; 7, 875-884) indicated that clopidogrel monotherapy was as effective as aspirin and dipyridamole combination therapy (Asasantin). The Committee considered that clopidogrel may be better tolerated than the combination therapy due to its better side-effect profile. The Committee

considered that clopidogrel monotherapy had the same or similar therapeutic effect as aspirin and dipyridamole combination therapy and that clopidogrel could be listed as an alternative if it was cost-neutral.

- 1.10 The Committee considered whether clopidogrel monotherapy could be used as an alternative to aspirin monotherapy in dipyridamole intolerant patients. The Committee noted that the European Stroke Organisation Guidelines for the management of ischaemic stroke and TIA (Cerebrovasc Dis 2008; 25; 5:457-507) states that clopidogrel is slightly more effective in preventing vascular events than aspirin as demonstrated by a 0.6% absolute risk reduction. The Committee noted that this was based on the CAPRIE (Lancet 1996; 348: 1329-1339) trial which comprised subgroups of patients with atherosclerotic vascular disease manifested as either recent ischaemic stroke, myocardial infarction, or symptomatic peripheral arterial disease. The Committee noted that when all the subgroups were grouped together, the patients treated with clopidogrel had a statistically significant absolute risk reduction of ischaemic stroke, myocardial infarction, or vascular death of 0.5% ( $p=0.043$ ) compared to the patients treated with aspirin. However, the Committee noted that when the stroke subgroup was considered alone, the result was not statistically significant ( $p=0.26$ ). The Committee concluded that in stroke and TIA patients, aspirin and clopidogrel have the same or similar therapeutic effect.
- 1.11 The Committee noted a recommendation by the authors of the 2008 New Zealand TIA Guidelines "For the Assessment and Management of People with recent transient ischaemic attack (TIA)" that aspirin and clopidogrel combination therapy be subsidised for 30 days in patients with, a high risk TIA in the last seven days, or two TIAs in the last seven days. The Committee noted that combination aspirin and clopidogrel therapy had been used in the EXPRESS study (Rothwell et al, 2007: Lancet; 370: 1432-1442) for 30 days. However, the Committee considered that as the study was designed to detect differences in outcomes with urgent assessment and immediate treatment rather than the effect of clopidogrel, and as this resulted in an increased use of standard medications, it was not possible to determine the effect of short-term clopidogrel therapy. The Committee considered that long-term use of clopidogrel and aspirin should not be used as it was not more effective than aspirin alone and it increased the risk of bleeding as shown in the MATCH (Diener et al, 2004: Lancet; 364: 331-337) and CHARISMA (Bhatt et al, 2006: NEJM; 354: 1706-1717) trials. The Committee considered that urgent assessment and treatment was important and that making clopidogrel available for a short period would encourage this. The Committee also considered that the use of the ABCD2 score would assist in identifying patients who need urgent attention. The Committee considered that aspirin and clopidogrel combination therapy, to be followed by ongoing aspirin and/or dipyridamole therapy, should be subsidised for 30 days in patients with a high risk TIA within the last seven days (high risk being defined as an ABCD2 score of four or more), or two TIAs in the last seven days. The Committee gave this recommendation a low to medium priority.

### **Acute Coronary Syndrome and Revascularisation Procedure**

- 1.12 The Committee noted that currently the duration of clopidogrel usage for acute coronary syndrome/revascularisation procedure is three months, while the duration is six months following the insertion of a stent.

- 1.13 The Committee noted that the three month duration for coronary syndrome/revascularisation was based upon this being the most cost-effective treatment duration at the time of listing given the high price of clopidogrel and that the majority of the benefit of clopidogrel is provided in the first three months as shown in the CURE study (Yusuf et al, 2001: NEJM; 345, 7, 494-502).
- 1.14 The Committee noted that it had previously recommended increasing the treatment duration for a drug-eluting stent from six months to 12 months with a low priority, despite the lack of appropriate evidence, based upon the high prevalence of myocardial infarction (MI) or death after late stent thrombosis and the low fiscal impact.
- 1.15 The Committee noted that the price of clopidogrel has reduced significantly from when it was first listed.
- 1.16 The Committee noted that the CURE study indicated that the benefit of clopidogrel could be extended to 12 months.
- 1.17 The Committee noted that 12 months clopidogrel treatment for acute coronary syndrome and following the insertion of a stent was consistent with international Guidelines.
- 1.18 The Committee concluded that there was no clinical reason not to extend the duration of clopidogrel treatment to 12 months for acute coronary syndrome and following a revascularisation procedure including the insertion of a stent. The Committee gave a low priority for this recommendation.

#### **Aspirin intolerant patients**

- 1.19 The Committee noted that currently clopidogrel is available for aspirin allergic patients (a history of anaphylaxis, urticaria or asthma following the ingestion of aspirin NSAIDs or other salicylates) but not aspirin intolerant patients due to GI bleeding.
- 1.20 The Committee noted the high priority of the August 2008 Cardiovascular Subcommittee to widen clopidogrel access to patients intolerant to aspirin therapy.
- 1.21 The Committee noted that for patients with previous peptic ulcer bleeding, aspirin plus a proton pump inhibitor (PPI) resulted in less recurrent ulcer bleeding than clopidogrel (Chan et al, 2005: NEJM; 352; 3, 238-244).
- 1.22 The Committee noted that in patients with stable aspirin induced peptic ulcer disease, there is no difference in dyspepsia symptoms and recurrence of ulcers if aspirin plus a PPI or clopidogrel plus a PPI is used based on a small randomised trial (Ng et al, 2004: Aliment Pharmacol Ther; 19, 359-365).
- 1.23 The Committee noted that recent evidence suggests that clopidogrel may be less effective when it is taken with a PPI (29 May 2009 Public statement by the European Medicines Agency on a possible interaction between clopidogrel and proton pump inhibitors).
- 1.24 The Committee considered that the current access to clopidogrel for aspirin allergic patients was appropriate and that it should not be widened to include aspirin intolerance due to GI bleeding. However, the Committee acknowledged that there are other forms of

aspirin intolerance, than allergy and GI bleeding, and that access to clopidogrel could be determined via a Special Authority waiver or it could be widened depending upon the price of clopidogrel, the fiscal risk and its cost-effectiveness.

## 2 COX-2 Inhibitors for Severe Haemophilia Complicated by Arthropathy

### Application

- 2.1 The Committee reviewed an application from [ withheld under s9(2)(a) of the OIA ] on behalf of the New Zealand Haemophilia Treaters Group for the listing of a COX-2 inhibitor agent on the Pharmaceutical Schedule for the treatment of haemophilic arthropathy associated with severe haemophilia.

### Recommendation

- 2.2 The Committee **recommended** that a COX-2 inhibitor be listed in the Pharmaceutical Schedule with a high priority for the treatment of haemophilic arthropathy associated with severe haemophilia.
- 2.3 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

- 2.4 The Committee noted that the application was for patients with haemophilic arthropathy associated with severe haemophilia and that severe haemophilia is defined as those with < 1% of normal circulating functional clotting factor. The Committee noted that those with moderate haemophilia are also prone to arthropathy and may need analgesic or anti-inflammatory treatment, but that this is generally less severe.
- 2.5 The Committee noted that haemophilia arthropathy is a very painful condition prone to recurrent bleeds, inflammation and further joint damage. The Committee noted that the greater life expectancy of patients with haemophilia means that even with good use of preventive measures, arthropathy can develop and also that joint damage is more likely to develop.
- 2.6 The Committee noted that the pain and inflammation in patients with haemophilic arthropathy associated with severe haemophilia are currently inadequately controlled with treatments such as paracetamol and opioids, and that aspirin and non-steroidal anti-inflammatory analgesic drugs (NSAIDs) are not used in practice as they are considered to increase the risk of bleeding and consequently the amount of factor replacement used.
- 2.7 The Committee noted that there is evidence that COX-2 inhibitors reduce pain and inflammation and result in less bleeding than conventional NSAIDs in other high risk patient groups.

- 2.8 The Committee noted a small randomised controlled trial by Tsoukas et al (Blood 2006: 107; 1785-1790) examining the effect of COX-2 inhibitors versus placebo in patients with haemophilic arthropathy (60%-70% of patients had severe haemophilia) with a history of joint bleeding and chronic symptomatic pain in one or more joints on 20 of 30 days prior to enrolment. The Committee noted that COX-2 inhibitors resulted in significant improvement in all endpoints (patient assessment of arthropathy pain and disease status and investigator assessment of disease status) versus placebo ( $p < 0.001$ ), that fewer patients taking a COX-2 discontinued due to a lack of efficacy ( $p = 0.048$ ), and that the incidence of joint bleeding was similar (66.7% versus 72.6%).
- 2.9 The Committee noted that there are no clinical trials comparing COX-2 inhibitors with NSAIDs in severe haemophilia arthropathy particularly assessing efficacy and safety. The Committee considered that such studies on people with severe haemophilia would be considered to be very risky.
- 2.10 The Committee noted that joint replacements were last line treatment and were very expensive, especially with the use of factor replacement (particularly in those with clotting factor inhibitors), with variable results. The Committee considered that the use of COX-2 inhibitors may delay surgical intervention, but would not replace it.
- 2.11 The Committee considered that the patient population was small, less than 100 patients, and therefore the fiscal risk was low.
- 2.12 The Committee considered that treatment with COX-2 inhibitors should be available, via Special Authority, for patients with severe haemophilia complicated by arthropathy.
- 2.13 The Committee considered that any of the available COX-2 inhibitors are likely to be appropriate.

### **3 Ambrisentan (Volibris) for Pulmonary Arterial Hypertension**

#### **Application**

- 3.1 The Committee reviewed an application from GlaxoSmithKline for the listing of ambrisentan (Volibris) on the Pharmaceutical Schedule for the treatment of pulmonary arterial hypertension (PAH) under the current PAH Special Authority Criteria.

#### **Recommendation**

- 3.2 The Committee **recommended** that ambrisentan is listed in the Pharmaceutical Schedule under the current PAH Special Authority Criteria with a medium priority.
- 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* v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

## Discussion

- 3.4 The Committee noted that bosentan, iloprost and sildenafil were listed on the Pharmaceutical Schedule, fully funded under Special Authority from July 2009.
- 3.5 The Committee noted that ambrisentan is an endothelin receptor antagonist, but not a dual endothelin receptor antagonist like bosentan. The Committee noted that the ET<sub>A</sub>:ET<sub>B</sub> selectivity of bosentan and ambrisentan is 30:1 and 4000:1 respectively, making ambrisentan a selective ET<sub>A</sub> receptor antagonist.
- 3.6 The Committee noted the placebo controlled ARIES 1 (Oudiz et al. 2006; Chest. 130: 4, Supplement , pp. 121S) and ARIES 2 (Unpublished clinical study report AMB-321) trials, and the ARIES C integrated analysis of these two trials (Galie et al. 2008: Circulation: 117. pp. 3010-3019).
- 3.7 The Committee noted that there are no trials that directly compare ambrisentan with bosentan and that the supplier had attempted to make indirect comparisons using the ARIES C trial and the AC-351 (Channick et al. 2001: Lancet. 359: pp. 1119-1123) and AC-352 (Rubin et al. 2002. NEMJ. 346: 12, pp.893-903) bosentan trials.
- 3.8 The Committee considered that ambrisentan improves patients' six minute walk tests (6MWT) (primary end-point in both trials) and that it has a similar adverse effect profile to bosentan, although the incidence of peripheral oedema appears higher with ambrisentan.
- 3.9 The Committee noted the supplier's claim that receptor selectivity is important although overall clinically relevant differences in receptor selectivity have not been demonstrated. With respect to drug metabolism and interactions the Committee noted the supplier's claim that this provides an advantage for ambrisentan over bosentan due to less hepatotoxicity and lack of interaction with sildenafil or warfarin. However, the Committee considered that hepatotoxicity may be a class effect and there has been no convincing evidence that drug interaction between bosentan, sildenafil and warfarin is a clinically relevant factor.
- 3.10 The Committee noted that the periodic safety update report (June 2007-2008) provided was only in summary form and considered that the supplier should supply the two year periodic safety update report data when it is available. The Committee also considered that additional long-term data should be supplied including the ARIES E trial and other ongoing phase two and three trials.
- 3.11 The Committee concluded that ambrisentan and bosentan have the same or similar clinical effect but that ambrisentan had a small cost advantage.

## 4 Aliskiren (Rasilez) for Hypertension

### Application

- 4.1 The Committee reviewed an application from Novartis New Zealand Limited for the listing of aliskiren (Rasilez) on the Pharmaceutical Schedule for the treatment of hypertension.

## Recommendation

- 4.2 The Committee **recommended** that the Application for aliskiren be declined due to a lack of long-term efficacy and safety data.
- 4.3 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.*

## Discussion

- 4.4 The Committee noted that aliskiren is an antihypertensive agent of the direct renin inhibitor class.
- 4.5 The Committee noted several studies comparing blood pressure reduction when using aliskiren compared to other antihypertensive agents including ramipril (Andersen et al, 2008, Journal of Hypertension 26: 589-599), losartan (Praving et al, 2008, NEJM 358: 2433-46), hydrochlorothiazide (Schmieder et al, 2007; Circulation 119: 417-425), amlodipine (Drummond et al, 2007; Journal of Clinical Hypertension 9: 742-750) and irbesartan (Gradman 2005, Circulation 111: 742-750).
- 4.6 The Committee noted the Canadian Expert Drug Advisory Committee (June 2008) concluded that while aliskiren reduces blood pressure in short-term trials there is no long-term evidence that this translates into improved cardiovascular, cerebrovascular or renal outcomes.
- 4.7 The Committee noted the Scottish Medicines Consortium (December 2008) recommended that aliskiren not be funded, as, while aliskiren showed comparable efficacy to other antihypertensives, its effects on mortality and morbidity were unknown.
- 4.8 The Committee considered that the short-term efficacy of aliskiren is comparable to other antihypertensive agents, but that there is no long-term efficacy and safety data with regard to clinically important endpoints.

## 5 Riluzole (Rilutek) for Amyotrophic Lateral Sclerosis

### Application

- 5.1 The Committee reviewed an application from Sanofi-Aventis New Zealand Limited for the listing of riluzole (Rilutek) on the Pharmaceutical Schedule for the treatment of amyotrophic lateral sclerosis.

### Recommendation

- 5.2 The Committee **recommended** that the Application for riluzole (Rilutek) for the treatment of amyotrophic lateral sclerosis be declined, because of its poor efficacy, high cost and poor cost effectiveness.

- 5.3 The Decision Criteria particularly relevant to this recommendation are: (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**

- 5.4 The Committee noted that amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease, for which there are no currently funded treatments. The Committee considered that there was an unmet clinical need for an effective treatment for ALS.
- 5.5 The Committee considered that there is moderate evidence that riluzole provides a short-term improvement in survival, together with a small gain in bulbar and limb function, based on results from two pivotal randomised controlled trials conducted in patients <75 years of age with less than five years' duration of symptoms and a vital capacity greater than 60% predicted (Bensimon et al. N Engl J Med 1994;330:585-91; Lacomblez et al. Lancet 1996;347:1425-31).
- 5.6 The Committee noted that in the Cochrane review of riluzole (Miller et al. Cochrane Database of Systematic Reviews 2007, Issue 1) it was estimated that riluzole improved survival by 2.3 months, based on the results of the abovementioned randomised trials. However, when the results of a third study where patients did not meet the same inclusion criteria, were included in the analysis there was no statistically significant difference in survival between patients treated with riluzole or placebo.
- 5.7 The Committee noted that the supplier had provided a fourth randomised controlled trial (Yanagisawa et al. Igakuno Ayumi 1997;182:851-66); however, it was in Japanese and as no translation had been provided it was not possible to evaluate it.
- 5.8 The Committee noted that riluzole was associated with side effects of nausea and asthenia, and severely abnormal liver function tests (LFTs) occur in 10% of patients, which necessitates monitoring. The Committee noted that any increase in survival with riluzole would be associated with an increase in healthcare costs for the duration of the extension in survival, given that most patients would remain in a very poor health state.
- 5.9 The Committee considered that, if funded, riluzole would be unlikely to affect the market dynamics of any other currently funded pharmaceutical.
- 5.10 The Committee considered that it was not possible to determine the likely average length of treatment from the information provided; however, a reasonable estimate would be between 12 and 18 months.
- 5.11 The Committee considered that the average dose of riluzole would be 100 mg per day (50 mg bid) and there was no evidence to support a benefit from a dose of 50 mg per day.
- 5.12 The Committee considered that, based on the evidence provided, the optimum time to start treatment would be as soon as diagnosis was made; based on New Zealand data this would be a median of 10 months after symptoms first appear. The Committee noted

that there was no evidence of benefit in patients starting riluzole more than five years from symptom onset.

- 5.13 Based on the results of the pivotal trials, the Committee considered that the patient group which might most benefit from riluzole would be those <75 years of age with less than five years' duration of symptoms and a vital capacity greater than 60% predicted.
- 5.14 The Committee noted that a rapid cost-utility analysis performed by PHARMAC staff suggested that riluzole has a relatively high cost per quality-adjusted life year (QALY).
- 5.15 The Committee considered that due to the high cost of riluzole, and poor cost effectiveness, riluzole should be subject to Special Authority restrictions if it was funded. The Committee considered that the restrictions proposed by the supplier seemed reasonable, although members noted that there was no evidence of benefit in patients >75 years of age.

## **6 Thalidomide for the Treatment of Patients with Newly Diagnosed Multiple Myeloma**

### **Application**

- 6.1 The Committee considered an application from Celgene Pty Ltd for the funding of thalidomide to be widened to include treatment of patients newly diagnosed with multiple myeloma.
- 6.2 The Committee noted that first line treatment comprised two distinct populations:
  - 6.2.1 Stem cell transplant ineligible patients, and
  - 6.2.2 Stem cell transplant eligible patients.

### **Recommendations - Stem cell transplant ineligible patients**

- 6.3 The Committee **recommended** that the Special Authority for thalidomide should be widened to include first line treatment of multiple myeloma in patients ineligible for stem cell transplantation. The Committee gave this recommendation a high priority.
- 6.4 The Committee further **recommended** that the application be reviewed by the Cancer Treatments Subcommittee of PTAC (CaTSoP) for advice regarding appropriate Special Authority criteria for transplant ineligible patients, thalidomide dosing/number of treatment cycles, and cost utility inputs.
- 6.5 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.*

## **Recommendation - Stem cell transplant eligible patients**

- 6.6 The Committee **recommended** that application for thalidomide in stem cell transplant eligible patients be declined.
- 6.7 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,*

## **Discussion**

- 6.8 The Committee noted that multiple myeloma is a relatively rare, cancer of the plasma cells predominantly affecting older people. Members noted that the median age at diagnosis is late 60s and that the incidence of multiple myeloma is approximately 40% higher in males than females. Members further noted that Maori have a substantially higher risk of being diagnosed with, and dying from, multiple myeloma than non-Maori. The Committee noted that listing thalidomide as a first line treatment would not necessarily improve access for Maori with multiple myeloma.
- 6.9 The Committee noted that multiple myeloma was an incurable disease with current treatment options providing median overall survival of around three years.
- 6.10 The Committee noted that current first line treatment options for multiple myeloma are dependent on the age of the patient and eligibility for stem cell transplantation. Members considered that currently in New Zealand, newly diagnosed patients with multiple myeloma aged under 65 years and otherwise healthy patients aged over 65 years would typically receive high dose induction chemotherapy (e.g. VAD, vincristine, adriamycin and dexamethasone) followed by a stem cell transplant as first line treatment. Members further considered that transplant ineligible patients would generally receive prednisone and melphalan as first line treatment.
- 6.11 The Committee noted that thalidomide was currently funded for patients who have received prior chemotherapy with refractory, progressive or relapsed multiple myeloma, i.e. second line treatment. Members noted that in the second line setting thalidomide is usually administered in conjunction with steroids (often dexamethasone) and sometimes with oral chemotherapy (e.g. cyclophosphamide), and typically administered at a dose of 100 mg per day.
- 6.12 The Committee noted that the supplier's application was for the funding of thalidomide to be widened to include treatment of patients newly diagnosed with multiple myeloma. Members noted that this would encompass first line treatment in two distinct populations:
- 6.12.1 Stem cell transplant ineligible patients – where thalidomide would be added to melphalan and prednisone.

6.12.2 Stem cell transplant eligible patients – where thalidomide in combination with dexamethasone would substitute for other induction chemotherapy regimens, mainly VAD (vincristine, adriamycin (doxorubicin) and dexamethasone).

6.13 The Committee discussed efficacy data for the two populations separately.

*Stem cell transplant ineligible patients*

6.14 The Committee reviewed evidence from five randomised controlled studies comparing melphalan and prednisone (MP) with and without thalidomide. Members noted that the studies were typically in older patients but that the study designs, populations enrolled (including prior treatment exposure) and treatment arms were somewhat heterogeneous.

6.15 The Committee noted that in these studies the dose of thalidomide varied (between 100 mg to 400 mg per day), however, the datasheet recommended dose of thalidomide was 200 mg per day for a maximum 12 cycles of six weeks in combination with melphalan and prednisone. The Committee considered that some patients, in particular the more elderly, may be treated with 100 mg per day thalidomide.

6.16 The Committee considered that despite heterogeneity of the studies, overall the data indicated that the addition of thalidomide to MP resulted in statistically significant improvements in overall survival, progression free survival and the proportion of patients with a treatment response, which ranged from 42% to 76%.

6.17 The Committee reviewed evidence from a meta-analysis of three of the randomised controlled studies (Hicks, L et al (2008). "A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma." Cancer Treatment Reviews. 34 (5): 442-452). Members noted that in this meta-analysis the addition of thalidomide to MP was associated with a statistically significant benefit in overall survival Hazard ratio 0.62 (95% confidence interval 0.50, 0.77).

*Stem cell transplant eligible patients*

6.18 The Committee considered that approximately half of all patients with newly diagnosed multiple myeloma may be eligible for a stem cell transplant. Members reviewed evidence from four randomised controlled studies, one of which had only been published in abstract form. Members considered that the study designs and populations enrolled were somewhat heterogeneous.

6.19 The Committee considered that whilst the studies generally demonstrated an improvement in response with thalidomide containing induction regimens, interpretation of longer term outcome data, including overall survival, was confounded by patients having received a transplant and subsequent (uncontrolled) treatments.

6.20 The Committee considered that whilst there may be some practical advantages to using an oral induction regimen (such as thalidomide plus dexamethasone) compared with currently used complex infusion regimens, the inability to determine the benefit of thalidomide on longer term outcomes prevented the Committee from making a positive recommendation for its use in this setting.

### *Toxicity of thalidomide*

- 6.21 The Committee noted that thalidomide is a known human teratogen and is therefore contraindicated in pregnant women and women of child-bearing potential must use two effective means of contraception. Members further noted that male patients with female partners of child bearing potential must use adequate contraceptive methods.
- 6.22 The Committee noted that thalidomide-treated patients reported more adverse events, including venous thromboembolism (VTE), peripheral neuropathy, constipation, somnolence and neutropaenia.
- 6.23 The Committee noted that VTE events were relatively common, as high as 23% of treated patients. Members noted that evidence from Hicks et al indicated that the risk of VTE can be reduced (but not eliminated) with low molecular weight heparin prophylaxis, such as enoxaparin. Members noted that peripheral neuropathy and constipation were more common than VTE, and although potentially less severe, these toxicities, and associated pain, may reduce patients overall quality of life significantly.
- 6.24 The Committee considered that the cost-utility analysis on thalidomide should take into account the costs and impact on quality of life of thalidomide-related toxicities given the high incidence, severity and clinical significance of these toxicities.

### *General discussion*

- 6.25 The Committee considered that multiple myeloma patients should be able to access funded thalidomide once in their treatment journey. Members considered that the evidence supported its use first line in stem cell transplant ineligible patients, but in the absence of clear data demonstrating an overall survival benefit it should remain funded as a second line treatment in patients who were eligible for first line treatment with induction chemotherapy and stem cell transplant.

## **7 Lenalidomide for Relapsed/Refractory Multiple Myeloma**

### **Application**

- 7.1 The Committee considered an application from Celgene Pty Ltd for the listing of lenalidomide (Revlimid 5 mg, 10 mg, 15 mg and 25 mg capsules) on the Pharmaceutical Schedule for the treatment of patients with relapsed/refractory multiple myeloma.

### **Recommendation**

- 7.2 The Committee **recommended** that the Application for lenalidomide be deferred pending a review of the Application by the Cancer Treatments Subcommittee.

### **Discussion**

- 7.3 The Committee noted that multiple myeloma is a relatively rare, cancer of the plasma cells predominantly affecting older people. Members noted that the median age at

diagnosis is late 60s and that the incidence of multiple myeloma is approximately 40% higher in males than females. Members further noted that Maori have a substantially higher risk of being diagnosed with, and dying from, multiple myeloma than non-Maori.

- 7.4 The Committee noted that multiple myeloma was an incurable disease with current treatments options providing median overall survival of around three years.
- 7.5 The Committee noted that thalidomide was currently funded for patients who have received prior chemotherapy with refractory, progressive or relapsed multiple myeloma, i.e. second line treatment. Members considered that current treatment options for thalidomide relapsed/refractory patients in NZ (i.e. third line treatment) include high dose dexamethasone alone, cyclophosphamide plus dexamethasone, or other chemotherapy regimens.
- 7.6 The Committee noted that lenalidomide is an analogue of thalidomide indicated, in combination with dexamethasone, for the treatment of multiple myeloma patients whose disease has progressed after one therapy. Members noted that lenalidomide's similar structure and function to thalidomide, and preclinical animal data, show it must be regarded as a potential human teratogen.
- 7.7 The Committee noted that the application comprised two discrete populations:
- 7.7.1 Lenalidomide for the treatment of patients who have failed one prior therapy (i.e. second-line treatment), and
  - 7.7.2 Lenalidomide for the treatment of patients who have failed one prior therapy (other than thalidomide) and have undergone, or are ineligible for, stem cell transplant, and have experienced subsequent treatment failure after a minimum of four weeks treatment with thalidomide (i.e. third-line treatment).
- 7.8 The Committee reviewed evidence from two phase III randomised placebo controlled trials comparing lenalidomide plus dexamethasone with dexamethasone alone in patients who had received at least one prior therapy: studies MM009 (Weber, D et al. 2007, New England Journal of Medicine 357(21): 2133-42) and MM010 (Dimopoulos, M et al. 2007, New England Journal of Medicine 357(21): 2123-32). Members also reviewed a pooled analysis of these two studies. Members noted that the majority of patients in both studies (>60%) had received two or more previous therapies.
- 7.9 The Committee noted that in both studies patients were randomised 1:1 to receive 25 mg lenalidomide or matching placebo on days 1 – 21 of a 28 day cycle, patients also received 40 mg of oral dexamethasone on days 1-4, 9-12 and 17-20 for the first four cycles, and days 1-4 of subsequent cycles. Treatment was continued until disease progression or unacceptable toxicity.
- 7.10 The Committee noted lenalidomide treatment was associated with venous thromboembolism, myelosuppression, and infections, however, neurotoxicity was lower than seen with thalidomide.
- 7.11 The Committee noted that the time to progression (TTP), the primary endpoint in both studies, was statistically significantly longer by about six months in patients treated with lenalidomide plus dexamethasone compared with those on dexamethasone alone.

- 7.12 The Committee further noted that overall survival was also improved, with an absolute difference of 8% in the pooled analysis and median overall survival increase of 3.7 months. However, the Committee noted that interpretation of the overall survival data was confounded by the unblinding of treatment assignment for all patients and patients in the dexamethasone alone arm being allowed to “cross-over” to lenalidomide plus dexamethasone.
- 7.13 The Committee considered that the study populations were not generally reflective of the proposed funding for lenalidomide in that the majority of patients (56% in 009 and 67% in 010) had not been previously exposed to thalidomide treatment.
- 7.14 The Committee reviewed evidence from a pooled analysis of 009 and 010 examining outcomes by prior thalidomide exposure (Wang et al Blood, 1 December 2008, Vol. 112, No. 12, pp. 4445-4451). Members noted that although the analysis was post hoc and therefore exploratory in nature, it was more reflective of the third line population for which lenalidomide funding was being sought.
- 7.15 The Committee noted more favourable efficacy results for thalidomide naïve patients compared with thalidomide-exposed patients were observed in both the lenalidomide plus dexamethasone group, and in the dexamethasone alone group. However, members considered the data demonstrated that lenalidomide treatment did improve outcomes, albeit to a lesser extent, in thalidomide-exposed patients. Complete response rate increased from 1.4% to 7.9% and median time to progression increased from 4.6 to 8.4 months.
- 7.16 The Committee noted that there was no evidence directly comparing lenalidomide with thalidomide in the second line setting. Members reviewed indirect comparisons provided by the supplier of data from studies 009 and 010 and two open label single arm studies of thalidomide plus dexamethasone in patients with relapsed/refractory multiple myeloma (Palumbo et al 2004 and Offidani et al 2007). Members considered that the evidence provided was weak and the two thalidomide studies were not particularly relevant to the funding application in that all patients enrolled were thalidomide naïve and the majority had received three or more prior treatments.
- 7.17 The Committee noted that lenalidomide was a very expensive, non-curative, treatment and its place in therapy was not clear from the evidence provided. Members specifically noted that the funding of lenalidomide would not address the disparity in multiple myeloma mortality in Maori compared with non-Maori, and that funding lenalidomide may actually inadvertently increase this disparity through the diversion of significant amounts of funding from early detection and treatment of multiple myeloma in this population

## **8 Bortezomib for Multiple Myeloma**

### **Application**

- 8.1 The Committee considered a cost utility analysis prepared by PHARMAC staff regarding the funding of bortezomib for the treatment of patients with relapsed/refractory multiple myeloma.

- 8.2 The Committee also considered information from clinicians and a patient regarding the use of bortezomib in multiple myeloma patients with renal impairment.

### **Recommendation**

- 8.3 The Committee **recommended** that bortezomib be listed as a second-line agent for patients with relapsed/refractory multiple myeloma. The Committee **recommended** that initial applications be valid for three months, with the requirement for a partial response to be demonstrated after four cycles for further approval to be granted. The Committee gave this recommendation a low priority.
- 8.4 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; (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**

- 8.5 The Committee noted that it had previously reviewed an application from Janssen-Cilag for the listing of bortezomib for the second-line treatment of multiple myeloma at its November 2008 meeting, where it deferred making a recommendation pending review by the Cancer Treatments Subcommittee and a PHARMAC cost-utility analysis (CUA). The Committee further noted that the application had subsequently been reviewed by the Cancer Treatments Subcommittee of PTAC at its February 2009 meeting; members reviewed the relevant minute.
- 8.6 The Committee noted correspondence from PHARMAC staff, clinicians and a patient regarding the use of bortezomib in patients with renal impairment. Members considered that although renal impairment was relatively common in multiple myeloma patients the relevant evidence for bortezomib was limited to a specific small group of patients with cast nephropathy. Members considered that although there was some evidence of benefit of bortezomib for these patients, the evidence was weak comprising small non randomised studies (largely case series).
- 8.7 The Committee reviewed a CUA provided by PHARMAC staff. Members noted that the CUA assumed a 20% absolute increase in progression-free and overall survival for bortezomib in combination with dexamethasone based on the results of the APEX study. Members considered that this was appropriate.
- 8.8 The Committee considered that patients would receive a maximum of eight treatment cycles of bortezomib in combination with dexamethasone. Members noted that there was a high drop-out rate in the APEX study due to toxicity. Members noted that the MedSafe approved datasheet recommends six cycles for responders and up to eight cycles for non-responders and considered that most prescribers would likely follow these recommendations.

- 8.9 The Committee considered that the duration of treatment for the comparator (thalidomide) was difficult to determine. Members considered that treatment duration would likely be limited by toxicities and considered that the majority of patients would not be treated for more than one year. Members recommended that PHARMAC staff review data from Pharmhouse to determine the current average duration of thalidomide treatment.
- 8.10 The Committee considered that following treatment with bortezomib patients with relapsed/refractory multiple myeloma would likely be treated with high dose chemotherapy plus dexamethasone or other new agents.
- 8.11 Overall, the Committee considered that the assumptions and inputs included in PHARMAC's CUA were appropriate.
- 8.12 The Committee considered that bortezomib was associated with some clinical benefit but it is very expensive. Members further noted that the single use vial containing 3.5 mg bortezomib was too big for the average patient (the recommended dose is 1.3 mg/m<sup>2</sup>, around 2.4 mgs for an average sized patient) and thus there is significant wastage associated with its use.

## 9 Sorafenib for the Treatment of Hepatocellular Carcinoma

### Application

- 9.1 The Committee considered an application from Bayer New Zealand Ltd for the listing of Sorafenib tosylate (Nexavar 200 mg table) on the Pharmaceutical Schedule for the treatment of patients for patients with hepatocellular carcinoma (HCC).

### Recommendation

- 9.2 The Committee **recommended** that application be **declined**.
- 9.3 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; (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

- 9.4 The Committee noted it had previously reviewed a funding application for sorafenib for advanced renal cell carcinoma (RCC); at the time PTAC considered that the cost of sorafenib was excessive for what is essentially a palliative treatment with significant toxicity and recommended that the application be declined.

- 9.5 The Committee noted that the supplier requests that sorafenib be funded for the treatment of patients with hepatocellular carcinoma (HCC), specifically patients with inoperable HCC with a Performance Status of zero to one.
- 9.6 The Committee considered that the majority of HCC is caused by persistent viral hepatitis infection; other risk factors include alcohol and tobacco use and exposure to aflatoxins. Members noted that the incidence of HCC in New Zealand is higher than in other Western countries, likely reflecting New Zealand's Asia-Pacific location and high incidence of viral hepatitis B and C infection.
- 9.7 The Committee reviewed evidence from a number of trials, with the key data being from two randomised, phase III studies comparing sorafenib with placebo: the SHARP study conducted in the USA, Europe, South America and Australia (Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol, study 100554, Llovet et al NEJM 2008, 359:378-90) and a study conducted in the Asian region (China, South Korea and Taiwan) (Chen et al Lancet Oncology 2009, 10:25-34).
- 9.8 The Committee noted that the SHARP study enrolled 602 patients with advanced HCC who were randomly assigned 1:1 to receive either sorafenib (400 mg twice daily, n=299) or placebo (n=303) with treatment continued until evidence of both radiological and symptomatic progression, unacceptable toxicity or death. Members noted that 47% of patients enrolled had hepatitis B or C. Members noted that the primary endpoint, overall median survival, was 10.7 months in the sorafenib group compared with 7.9 months in the placebo group (Hazard ratio 0.69, 95% CI 0.55-0.87,  $p < 0.001$ ) and survival rates at one year were 44% and 33%, respectively. Members noted, however, that no patients had a complete response to treatment and partial responses were observed in only 2% of sorafenib treated patients compared with 1% of placebo treated patients, the majority of patients (71% and 67% respectively) having stable disease.
- 9.9 The Committee noted that the Asian study, was very similar in design to the SHARP study, except that it randomised patients 2:1 to receive sorafenib (n=150) or placebo (n=76). Members noted that in this study more patients (73%) had hepatitis infection at baseline, however the patients were younger, median age 51 years, compared with 65 years in SHARP. Members noted that in this study overall median survival was 6.5 months in the sorafenib treated group compared with 4.2 months in the placebo group (Hazard ratio 0.68, 95% CI 0.50-0.93,  $p < 0.014$ ), time to progression was also longer in the sorafenib treated patients (2.8 months compared with 1.4 months,  $p = 0.0005$ ) but there was no difference in time to symptomatic progression (3.5 months compared with 4.3 months, HR 0.90 (95% CI 0.67-1.22,  $p = 0.50$ ). Overall survival was lower (53.3% vs 36.7% at six months in the sorafenib and placebo groups respectively), compared with SHARP, likely reflecting the more advanced population enrolled in the Asian study and worse prognosis associated with Hepatitis B infection. Members noted that, like SHARP no patients had a complete response to treatment and partial responses were observed in only five sorafenib treated patients (3.3%) compared with one placebo treated patient (1.3%), 54% of sorafenib treated patients had stable disease compared with 28% of placebo patients and 31% and 54% of patients had progressive disease respectively.
- 9.10 The Committee noted that sorafenib treatment was associated with diarrhoea, fatigue, hand-foot syndrome, weight loss and hypophosphatemia. In the two phase III studies 8%-10% of sorafenib patients experienced grade 3/4 hand-foot syndrome and 6-8% grade 3/4 diarrhoea.

- 9.11 The Committee noted the supplier provided a cost-effectiveness analysis, which indicated the cost per life year gained of sorafenib was in excess of \$85,000. The Committee noted that PHARMAC staff had estimated the cost per quality-adjusted life year (QALY) of sorafenib in HCC to be over \$120,000.
- 9.12 The Committee noted that sorafenib was a very expensive treatment for the limited benefit demonstrated. Members considered that funding would be better directed at both preventing and treating hepatitis B infection, thus reducing HCC incidence, rather than funding sorafenib treatment.

## 10 Budesonide (Entocort CIR) for Crohn's Disease, Microscopic Colitis and Graft versus Host Disease

### Application

- 10.1 The Committee reviewed an application from the New Zealand Society of Gastroenterology to widen access to budesonide (Entocort CIR) on the Pharmaceutical Schedule for the treatment of Crohn's disease and collagenous colitis and lymphocytic colitis (microscopic colitis).
- 10.2 In addition, the Committee reviewed a proposal from PHARMAC staff to widen access to budesonide (Entocort CIR) on the Pharmaceutical Schedule for the treatment of gut Graft versus Host disease.

### Recommendation

- 10.3 The Committee **recommended** that the Special Authority criteria for budesonide in Crohn's disease be amended to include patients with psychiatric problems and patients with relapse during pregnancy (where corticosteroids are considered to be contraindicated) with a high priority. In addition, the Committee **recommended** that the Special Authority criteria for budesonide be amended to include collagenous colitis and lymphocytic colitis (microscopic colitis) with a medium - high priority. Changes to the Special Authority are as follows (changes in bold and strikethrough):

#### 1. Crohn's Disease

Special Authority for Subsidy

Initial application from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:

Both:

Mild to moderate ileal, ileocaecal or proximal Crohn's disease; and

Any of the following:

2.1 Diabetes; or

2.2 Cushingoid habitus; or

2.3 Osteoporosis where there is significant risk of fracture; or

2.4 Severe acne following treatment with conventional corticosteroid therapy; or

**2.5 History of severe psychiatric problems associated with corticosteroid treatment; or**

- 2.6 History of major mental illness (such as bipolar affective disorder) where the risk of corticosteroid treatment causing relapse is considered to be high; or**  
**2.7 Relapse during pregnancy (where corticosteroids are considered to be contraindicated).**

Renewal from any relevant practitioner. Approvals valid for 3 months where the treatment remains appropriate and the patient is benefiting from treatment. The patient must have had no more than 1 prior approval in the last year.

Note: Clinical trials for Entocort CIR use beyond three months demonstrated no improvement in relapse rate.

## **2. Collagenous and Lymphocytic Colitis (Microscopic Colitis)**

### **Special Authority for Subsidy**

**Initial application from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criterion:**

**Diagnosis of microscopic colitis (collagenous or lymphocytic colitis) by colonoscopy with biopsies**

**Renewal from any relevant practitioner. Approvals valid for 3 months where the treatment remains appropriate and the patient is benefiting from treatment.**

- 10.4 The Committee **recommended** that access to budesonide for all other indications (namely steroid dependency where immunosuppression treatment has failed and attempts at steroid withdrawal have led to relapse, the extension of Special Authority initial and renewal approval period from three to six months, and gut Graft-versus-Host disease) be widened in the Pharmaceutical Schedule with a low priority.
- 10.5 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand, (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things, (iv) the clinical benefits and risks of pharmaceuticals, and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## **Discussion**

- 10.6 The Committee noted that it had previously reviewed the Special Authority criteria for budesonide on several occasions with the most recent review in 2005. The Committee noted that the ad-hoc Gastrointestinal Subcommittee of PTAC had considered the Special Authority criteria for budesonide in 2008 and considered that the renewal criteria could be removed and access widened to include use in microscopic colitis.
- 10.7 The Committee noted the Cochrane review of budesonide for use in Crohn's disease (Benchimol EI, Seow, CH, Otley AR, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD002913. DOI: 10.1002/14651858.CD002913.pub2). The Committee considered that there was no new evidence of significance provided for budesonide for its use in Crohn's disease.
- 10.8 The Committee considered that widening access to patients with steroid dependency where immunosuppressant treatment has failed and attempts at steroid withdrawal have

led to relapse does not appear consistent with the literature that shows steroids do not reduce relapse rates. The Committee however considered that there would be benefit in widening access to patients with severe psychiatric problems and relapse during pregnancy (where corticosteroids are considered to be contraindicated).

- 10.9 The Committee considered that there was insufficient evidence to indicate that patients may benefit from up to six months treatment with budesonide and that the current approval restriction of the Special Authority criteria to three months reinforces the evidence that budesonide is only effective for induction of remission (and remains inferior to prednisolone therapy).
- 10.10 The Committee noted that the incidence of microscopic colitis has been estimated by the New Zealand Society of Gastroenterology at 4-8 per 100,000 people. The Committee noted the interventions for treating collagenous colitis Cochrane review (Am J Gastroenterol. 2009 Jan;104(1):235-41; quiz 234, 242) and considered that the evidence for use of budesonide in collagenous colitis was good, but was weaker for lymphocytic colitis.
- 10.11 The Committee considered that budesonide may provide additional health benefit compared with other treatment options for patients with microscopic colitis as budesonide was likely to improve control of chronic gastrointestinal symptoms (Madish et al.; Int J colorectal Dis 2005;20:312-316). The Committee noted the study by Bonderup et al. (Gut 2009; 58:68-72) and considered that treatment of budesonide for collagenous colitis would likely be long-term given the chronic nature of the disease and the need to prevent relapse. Members noted that relapse after discontinuation for collagenous colitis and lymphocytic colitis was common although the relapse rate was lower (40%) for lymphocytic colitis than in collagenous colitis (Miehlke S, Madisch A, Bethke B, *et al*; Gastroenterology 2008;135:1510-6, 2008).
- 10.12 The Committee considered that budesonide may replace mesalazine or symptomatic therapies in treating microscopic colitis if access is widened. The Committee considered that no significant changes would result in usage if access was widened to include use in Crohn's disease patients with psychiatric problems or relapse during pregnancy.
- 10.13 The Committee noted several studies for the off-label indication for chronic gut Graft versus Host disease and considered the quality of evidence to be weak. The Committee noted that Ibrahim et al, (Biol Blood Marrow Transplant 15: 395-405 (2009) American Society for Blood and Marrow Transplantation) suggested that the outcome of various gut Graft versus Host disease treatment modalities remain far from satisfactory. The Committee noted a phase III trial (Hockenbery et al.; Blood, 2007; 109:4557-4563) that led to a non-significant result in patients with anorexia, vomiting and diarrhoea leading to the FDA not approving budesonide for gut Graft versus Host disease because of failure to meet the main study endpoint.
- 10.14 The Committee considered that there were no evidence of difficulties to access for alternative and effective therapies for microscopic colitis but that there were difficulties for finding therapies for gut Graft versus Host disease.

## 11 Insulin Glargine (Lantus) for Treatment of Diabetes Mellitus

### Application

11.1 The Committee considered a proposal from PHARMAC staff to remove the Special Authority for insulin glargine (Lantus) on the Pharmaceutical Schedule for the treatment of type 1 or type 2 diabetes mellitus patients who require insulin for the control of hyperglycaemia.

### Recommendation

11.2 The Committee **recommended** that the proposal to remove the Special Authority criteria for insulin glargine (Lantus) for the treatment of type 1 or type 2 diabetes mellitus patients who require insulin for the control of hyperglycaemia be **declined** until further evidence becomes available conclusively addressing the concerns that insulin glargine is associated with a potential increased incidence of cancer.

11.3 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.*

### Discussion

11.4 The Committee noted the four recently-published (26 June 2009) observational studies on the web site of the journal Diabetologia, discussing a potential association between the use of insulin glargine in people with type 2 diabetes and cancer risk. The Committee noted that these studies used registries covering 301,136 insulin-treated patients in Germany, Sweden and Britain and suggested insulin glargine may increase the risk of cancer, though the data is not conclusive. Members noted that the smallest but most methodologically sound study found no signs of a link. Members also noted that follow up periods in these studies were relatively short.

11.5 The Committee noted that the association was particularly for breast cancer, but the absolute risk was small. The largest German study found a difference of roughly one extra cancer diagnosed for every 100 people taking insulin glargine compared with those on human insulin. However, the Committee noted that the results depended on several adjustments to establish a “dose-for-dose” analysis. In the unadjusted analysis, people taking insulin glargine were less likely to develop cancer.

11.6 The Committee considered that the quality of evidence was poor and that the strength of association between glargine and cancer revealed in the studies was weak. The Committee considered that it could not confirm or exclude the risks highlighted from these studies.

11.7 The Committee considered the Bradford Hill criteria for assessing evidence of causation. The Committee noted that there is biological plausibility for a signal, insofar as insulin glargine associates more strongly with the known oncogenic IGF-1 receptor, notwithstanding that post-injection subcutaneous metabolism is considered to reduce this effect. The Committee noted that only the German study looked at a dose response

relationship and that a relationship was shown. Members considered that the strength of association between insulin glargine and cancer was weak with a hazard ratio of just above one.

- 11.8 The Committee considered that there were no issues with access to alternative and suitable insulin preparations on the Pharmaceutical Schedule. The Committee considered that the benefits of insulin glargine for patients with type 2 diabetes over human insulin are likely to be marginal and considered it would be better to target insulin glargine use to a selected group of these patients. The Committee considered that the Diabetes Subcommittee of PTAC would be best placed to define this group of patients.
- 11.9 The Committee noted that the studies had not proved possible to place insulin detemir under similar scrutiny, but it would be prudent for this insulin analogue to also be investigated in more detail by international researchers.
- 11.10 The Committee noted that Medsafe had not yet provided any recommendations or issued any warnings over the use of insulin glargine, however PHARMAC should monitor any advice from Medsafe on this issue.

## 12 Access to Treatments for Multiple Sclerosis

### Application

- 12.1 The Committee reviewed a submission from [redacted] withheld under s9(2)(a) of the OIA [redacted] relating to the multiple sclerosis (MS) treatments beta-interferon (interferon beta-1-alpha [Avonex] and interferon beta-1-beta [Betaferon]) and glatiramer acetate (Copaxone).

### Recommendation

- 12.2 The Committee **recommended** that PHARMAC staff perform a cost-utility analysis and bring it back to the Committee for review. The Committee suggested the analysis could include, in addition to the previous recommendations from the Committee regarding changes to the access criteria, the following scenarios: increasing the stopping criterion from an Expanded Disability Status Scale (EDSS) score of 6.0 to 7.0; treatment after the first demyelinating episode; treatment of secondary progressive MS; allowing treatment switching within a 24 month period without reapplication; allowing treatment with a second class of treatment when the stopping criteria are met on the first treatment.
- 12.3 The Committee **recommended** that this application be sent to the Multiple Sclerosis Treatments Assessments Committee along with this minute for its comment.

### Discussion

- 12.4 The Committee considered that the additional evidence provided regarding treatment of patients with secondary progressive MS was of modest quality and suggested that there

was a small reduction in the risk of deterioration with beta-interferon treatment in patients secondary progressive MS whose EDSS score at study entry was less than seven.

- 12.5 The Committee noted that there are no published meta-analyses that properly quantify this reduction in risk, and considered that it was unclear whether the risk difference is maintained over a time period greater than in clinical trials (two to three years).
- 12.6 The Committee noted that no evidence had been provided to suggest that glatiramer acetate provided a similar reduction in risk of deterioration.
- 12.7 The Committee noted that the applicants had provided additional evidence in support of the benefits of treatment with a second class of MS medication after failure of treatment (as defined by current access criteria) with the first class of treatment (referred to as “treatment switching”). The Committee noted that it had previously (in November 2008) recommended that the access criteria be amended to permit treatment switching in patients with a stable or increasing relapse rate over 12 months of treatment (compared with the relapse rate prior to starting treatment), provided that no other exit criteria (either current exit criteria or exit criteria modified as recommended by the Committee, below) are met, with a medium priority.
- 12.8 The Committee considered that the additional evidence in support of treatment switching was of modest strength, comprising a randomised controlled trial comparing beta-interferon with glatiramer acetate (i.e., not treatment switching) suggesting that the two treatments provide similar efficacy (Mikol et al. *Lancet Neurology* 2008;7:903-14), a narrative review discussing comparative efficacy of different treatments for multiple sclerosis (Goodin DS. *Neurology* 2008;71(Suppl 3):S8-S13) and a retrospective cohort study (Gajofatto et al. *Multiple Sclerosis* 2009; 15:50-58) which the Committee considered has a high risk of bias because there is no definition of treatment failure (other than the clinicians’ judgement) and very few patients had prolonged follow-up.
- 12.9 The Committee considered that insufficient evidence had been provided to support a change to its previous recommendation in relation to treatment switching.
- 12.10 The Committee noted that publication of the BEYOND trial would provide important information about the comparative efficacy of lower versus higher dose beta-interferon and glatiramer acetate.
- 12.11 The Committee considered that the applicants had provided very good evidence that prescription of beta-interferon reduces recurrence rate at one and two years in patients with one demyelinating episode, although no evidence was provided to demonstrate that this benefit was maintained in the longer term.
- 12.12 The Committee noted that according to a published study (Fisniku LK et al. *Disability and T2 MRI lesions: a 20-year follow up of patients with relapse onset multiple sclerosis. Brain* 2008;131:808-17), only 63% of patients with magnetic resonance imaging (MRI) changes and one demyelinating episode go on to develop MS, so if the criteria were amended to allow treatment in this patient group it would, potentially, result in 37% of patients unnecessarily receiving treatment. The Committee noted that this figure would reduce to 15% if access was limited to patients with more than nine lesions on MRI.

- 12.13 The Committee noted that the applicants were concerned at the apparent weight the Committee placed on changes in EDSS score. The Committee considered that there were always going to be limitations in any scoring system used to assess disease severity in MS; however, EDSS was currently the most widely used and had the most supporting evidence from clinical trials.
- 12.14 The Committee noted that the cost, and cost-effectiveness, of treatments are included in PHARMAC's decision criteria and, therefore, need to be taken into account in any recommendations made by the Committee. The Committee considered that it would be reasonable for PHARMAC staff to adapt the analysis of the School of Health and Related Research, Sheffield University, UK (SchARR) (conducted for the National Institute of Health and Clinical Excellence (NICE)) as the basis of its cost-utility analysis.
- 12.15 The Committee considered that it was likely that beta-interferon and glatiramer acetate would be superseded by natalizumab (Tysabri). The Committee noted that this was currently considered to be a hospital treatment and, therefore, its funding would not fall within the community Pharmaceutical Budget.