

PTAC meeting held 25 & 26 February 2010

(minutes for web publishing)

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

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

PTAC may:

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

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA):

- (a) in order to protect the privacy of natural persons (section 9(2)(a));
 - (b) to enable PHARMAC to carry out, without prejudice or disadvantage, commercial activities (section 9(2)(i));
 - (c) to enable PHARMAC to carry on, without prejudice or disadvantage, negotiations (including commercial and industrial negotiations (section 9(2)(j))).
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1 Minutes of PTAC Meeting Held November 2009

1.1 The Committee reviewed the record of the PTAC meeting held on 12 & 13 November 2009 and made the following minor amendment:

1.1.1 Etravirine – paragraph 4.5: replace “optimised NTRI” with “optimised NRTI”.

2 Subcommittee Records

2.1 Cancer Treatments Subcommittee (CaTSoP) Minutes – 20 November 2009

2.1.1 PTAC considered the rabbit anti-thymocyte globulin (ATG) minute for Graft Versus Host Disease (GVHD) prophylaxis, and noted that in Australia rabbit ATG was more expensive than equine ATG. The Committee considered that it was unexpected for rabbit ATG to be cheaper than equine ATG and recommended that PHARMAC staff check the pricing. It further **recommended** that if rabbit ATG was cheaper than equine ATG, then it agreed with CaTSoP’s recommendation in point 6.10.9 to list rabbit ATG.

2.1.2 PTAC considered the gemcitabine and vinorelbine minute for Hodgkin’s disease, and noted CaTSoP’s recommendation at point 7.7, to fund this combination therapy with a medium priority. PTAC further noted that PHARMAC had already progressed this recommendation and it was currently under consultation.

2.1.3 PTAC considered the gemcitabine and vinorelbine minute for T-cell lymphoma, and noted CaTSoP’s recommendation at point 7.14, to fund for up to six cycles, patients with T-cell lymphoma who fail to respond to second-line salvage chemotherapy or those who relapse after transplantation (i.e. in the third-line setting), with a medium priority. PTAC agreed with CaTSoP’s **recommendation** subject to a favourable cost utility analysis.

2.1.4 PTAC considered the lenalidomide minute for relapsed/refractory multiple myeloma and noted CaTSoP’s recommendation at point 9.9, which recommended lenalidomide be funded for second-line treatment with a low priority. PTAC accepted CaTSoP’s recommendation.

withheld under s9(2)(i) and/or s9(2)(j) of the OIA

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2.1.5 The Committee noted and accepted the remainder of the record of the Subcommittee meeting.

2.2 Special Foods Subcommittee – 14 October 2009

2.2.1 The Committee noted and accepted the record of the Subcommittee meeting.

2.3 Special Foods Subcommittee – 2 December 2010

2.3.1 The Committee noted and accepted the record of the Subcommittee meeting.

3 Isopropyl Alcohol and Anhydrous Glycerine (EarClear) for Swimmers Ear

- 3.1 The Committee considered a funding application for EarClear, isopropyl alcohol and anhydrous glycerine, from Wilson Consumer Products, NZ, and additional clinical advice from [withheld under s9(2)(a) of the OIA] and [withheld under s9(2)(a) of the OIA]. The Committee noted the clinical advice recommended that this product was a drying agent for swimmers ear and that there was already a drying solution listed on the Pharmaceutical Schedule for this condition. The clinical advice further recommended that this product should remain an over-the-counter product and not be listed on the Pharmaceutical Schedule.
- 3.2 The Committee agreed with the clinical advice that PHARMAC had received, and **recommended** that the application be declined.
- 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (vii) The direct cost to health service users (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

4 Dornase Alpha for Cystic Fibrosis

Application

- 4.1 The Committee reconsidered an application from the Cystic Fibrosis Advisory Panel (the Panel) to amend the dornase alfa Special Authority criteria.

Recommendation

- 4.2 The Committee **deferred** making a recommendation and requested further information from the Panel regarding the proposal, including how hypertonic saline could be incorporated into the criteria and whether the response parameters proposed for one month trials are meaningful.

Discussion

- 4.3 The Committee noted that it had previously accepted that there was evidence for benefit in patients with mild disease and had recommended that the requirement for patients to have an FEV₁ less than 65% of predicted be removed from the criteria.

- 4.4 The Committee noted that the Panel had confirmed most studies measured response relative to baseline and that relative response has always been used when determining whether patients qualified for ongoing therapy. Members considered that the criteria should be clear on whether response is measured in litres or percent predicted and considered that it may be useful to include the equation used to calculate response in the criteria.
- 4.5 The Committee considered that the requirement for a one month review should be retained in the criteria and that revised response parameters dependant on baseline lung function seemed reasonable. Members discussed whether the response requirements proposed by the Panel were meaningful, noting that the Cobos paper classified an improvement in FEV₁ of 0-10% as “insignificant” (Cobos et al. Eur J Pediatr 2000; 159:176-181). Members considered that an increase in FEV₁ of 3% after one month would likely be within the normal variability observed in patients with cystic fibrosis and questioned whether this was a meaningful response.
- 4.6 Members noted that the reference equations used to determine percent predicted varied throughout the country and that this may have a significant effect on percent predicted values reported in applications.
- 4.7 The Committee considered that the use of hypertonic saline should be included in the criteria and considered that the Panel should consider this further, noting the Australian study (Elkins et al. N engl J Med 2006;354;229-40). PHARMAC staff noted that the Panel had previously recommended including a criterion regarding previously having trialled hypertonic saline but that this had not yet been formally incorporated into the criteria. Members considered that all patients should be required to have trialled hypertonic saline before being eligible for a trial of dornase alpha.
- 4.8 The Committee considered that the requirement for a six month review should be retained in the criteria. Members considered that the six month review helps to ensure compliance and is also useful to identify non-responders. Members noted PHARMAC’s data which suggested that approximately 15% of responders at one month were non-responders at six months.
- 4.9 The Committee considered that it was important to rectify the potential misinformation in the Fuchs study (Fuchs et al. N Engl J Med 1994;331:672-3) relating to variability in FEV₁ results (misreported standard deviations), which had informed PHARMAC’s previous setting of eligibility criteria setting for dornase alpha, and suggested that PHARMAC staff write to the New England Journal of Medicine asking that this be resolved and publicised.

5 Fenofibrate

Application

- 5.1 The Committee reviewed an application from [withheld under s9(2)(a) of the OIA] for the listing of fenofibrate on the Pharmaceutical Schedule based on the results of the FIELD

and DIAS studies. The Committee noted that [

withheld under s9(2)(a) of the OIA]

Recommendation

5.2 The Committee **recommended** that the Application for fenofibrate be declined.

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

Discussion

- 5.3 The Committee noted that the basis for the application from [withheld under s9(2)(a) of the OIA] was that the FIELD study and the DIAS study provide evidence that fenofibrate is associated with long-term renal protection. The Committee noted that [withheld under s9(2)(a) of the OIA] considered that renal protection data is not available for the currently listed bezafibrate or the currently unlisted gemfibrozil and that fenofibrate would be a useful option for the treatment of lipid abnormalities and for the prevention of micro vascular complications in patients with type 2 diabetes.
- 5.4 The Committee noted a number of studies including the FIELD trial (Keech et al. Lancet 2005;366:1849-61; Keech et al. Lancet 2007;370:1687-97; Rajamani et al. Lancet 2009;373:1780-8), and the Diabetes Atherosclerosis Intervention Study (DIAS) (Steiner et al. Lancet 2001;357:905-10; Ansquer et al. Am J Kidney Dis 2005;45:485-93).
- 5.5 The Committee noted that while the FIELD trial indicated that fenofibrate, when compared to placebo, did not reduce the risk of coronary events (the primary outcome) in patients with type 2 diabetes mellitus, it did reduce a number of secondary outcomes including non fatal myocardial infarctions, and tertiary outcomes including the number of minor and first amputations, and the need for laser treatment for diabetic retinopathy. The Committee also noted two sub studies involving the Helsinki FIELD cohort (Forsblom et al. Diabetes Care. 2010;33:215-220; Hiukka et al. J. Am. Coll. Cardiol. 2008;52:2190-2197) which failed to show reno-protective effects or reduction of carotid intimal medial thickness. In addition, the Committee questioned the accuracy of urinary albumin measurement and the lack of hard outcomes such as reduction in end stage renal failure with fenofibrate.
- 5.6 The Committee noted the Diabetes Atherosclerosis Intervention Study which indicated that fenofibrate reduces the angiographic progression of coronary-artery disease and reduced the progression from normal albumin excretion to microalbuminuria when compared to placebo. Again, the Committee considered that there was a lack of hard cardiovascular and renal outcomes data.
- 5.7 The Committee noted that there is a lack of similar studies using bezafibrate or gemfibrozil and that there is a lack of head to head studies comparing the effect of bezafibrate, gemfibrozil and fenofibrate. The Committee noted that the best hard endpoint evidence for cardiovascular outcomes is available for gemfibrozil, although it noted that a recent post hoc analysis of the BIP trial (Goldenberg et al. J. Am. Coll.

Cardiol. 2008;51:459-465) also indicated that cardiovascular benefits occur with bezafibrate when following adjusted for statin contamination.

- 5.8 The Committee considered that the evidence of any benefit for fenofibrate was modest and that it was likely that any benefit would also occur with the use of other fibrates. The Committee considered that statins remain the primary agent for lipid control in type 2 diabetics and that fibrates are a useful second line option.
- 5.9 The Committee considered that the benefits of fenofibrate in preventing micro vascular complications might be independent to its lipid lowering effects. The Committee considered that it would be difficult to target patients for the prevention of micro vascular complications and considered that most of the patients with type 2 diabetics could potentially use fenofibrate for this and that this could be a significant fiscal risk.
- 5.10 The Committee also noted that the Cardiovascular Subcommittee of PTAC had recommended that gemfibrozil is re-listed on the Pharmaceutical Schedule with a medium priority and that PHARMAC staff had recently received a tender bid for the supply of gemfibrozil.
- 5.11 The Committee noted that fenofibrate was not registered in New Zealand and was likely to be significantly more expensive than either bezafibrate or gemfibrozil. The Committee also noted that gemfibrozil was currently registered and a supplier was available. The Committee therefore considered that gemfibrozil was a preferable alternative to fenofibrate and that if gemfibrozil was listed, then fenofibrate would not be required. However, the Committee considered that it may be appropriate to reconsider the role of fenofibrate following the publication of the ACCORD trial results¹.

6 Prasugrel hydrochloride (Effient) for patients who are to undergo Percutaneous Coronary Intervention

Application

- 6.1 The Committee reviewed an application from Eli Lilly for the listing of prasugrel hydrochloride (Effient) on the Pharmaceutical Schedule for the treatment of patients undergoing percutaneous coronary intervention.

Recommendation

- 6.2 The Committee **recommended** that the Application for prasugrel hydrochloride (Effient) for the treatment of patients undergoing percutaneous coronary intervention be declined.

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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than*

¹ At its May 2010 meeting, PTAC noted that the ACCORD trial referred to in its minute on 25 & 26 February was now published, and that the study had reported a negative outcome. The Committee **recommended** that, further to its minute of February 2010, paragraph 10.11, there was no need for it to review fenofibrate again at this time.

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

- 6.3 The Committee noted that the application was for 15 months of prasugrel in combination with aspirin for patients less than 75 years of age, with a body weight greater or equal to 60 kg, and with no prior history of stroke or transient ischemic attack, where the patient is undergoing percutaneous coronary intervention and has ST-segment elevation myocardial infarction, stent thrombosis during clopidogrel treatment, or diabetes mellitus.
- 6.4 The Committee noted that the application was based on the TRITON-TIMI 38 trial (Wiviott et al. NEJM 2007;357:2001-15) and a number of sub analyses including in patients with ST-segment elevation myocardial infarction (Montalescot et al. Lancet 2009;373:723-731), coronary stent insertion (Wiviott et al. Lancet 2008;371:1353-63) and diabetes (Wiviott et al. Circulation 2008;118:1-12).
- 6.5 The Committee noted that TRITON-TIMI-38 compared prasugrel (60-mg loading dose and 10-mg daily maintenance for 6-15 months) with clopidogrel (300-mg loading dose and 75-mg daily maintenance for 6-15 months). After 15 months the absolute risk reduction with prasugrel for the primary endpoint (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) was 2.2% in the overall cohort, 2.4% in patients with ST-segment elevation myocardial infarction, 1.8% with stent insertion, and 4.8% in patients with diabetes. The Committee considered that overall, prasugrel offered a modest benefit with an increased risk of haemorrhage.
- 6.6 The Committee noted a number of weaknesses with the TRITON-TIMI 38 trial and its interpretation including; the main difference being the incidence of non-fatal myocardial infarction although these were determined by the use of biochemical/ECG criteria and it is not clear how many were clinically significant, the clopidogrel loading dose was given during PCI in the trial whereas in clinical practice it is given prior to PCI, the faster onset of action of prasugrel biasing the early results towards prasugrel, the potential for a higher loading dose of clopidogrel to be used in clinical practice, the optimal treatment duration being unknown, uncertainty about the balance of efficacy and harm in some sub-groups such as older adults and those weighing less than 60 kg, and the lack of a significant interaction term in the diabetes subgroup even though superior efficacy is claimed.
- 6.7 The Committee noted that the Evidence Review Group (ERG) Report (6 April 2009) considered prasugrel and clopidogrel to be broadly equivalent in terms of clinical effectiveness.
- 6.8 The Committee noted that prasugrel is significantly more expensive than clopidogrel and that clopidogrel has been included in the current tender and therefore the price is likely to be significantly lower. The Committee therefore considered that the application could have a significant budget impact compared to clopidogrel even with the limited criteria indicated.
- 6.9 The Committee noted that the suppliers cost-utility analysis assumed that the incremental benefit provided by prasugrel continued for the life-time of the patient. The

Committee considered that there was no evidence to support the extrapolation of the incremental benefit of prasugrel beyond the 15 month trial period. It was noted that the incremental benefit of prasugrel was the greatest in the first month. The Committee noted that PHARMAC had assessed the cost-effectiveness of prasugrel compared with clopidogrel using a time horizon of 12 months, and that the resulting cost per quality-adjusted life year (QALY) was very high in the target patient population.

- 6.10 The Committee noted that potential patient groups which may benefit from treatment with prasugrel included patients allergic to clopidogrel, patients who had a stent thrombosis while using clopidogrel, and patients who did not respond to clopidogrel due to polymorphisms of CYP2C19 and CYP2C9. However, the Committee considered that clopidogrel allergy is rare noting there were no reported cases in the large clopidogrel trials. The Committee considered that although it may seem reasonable to consider prasugrel in patients with stent thrombosis on clopidogrel, there is no direct randomised trial evidence to support this. However, the Committee considered that it would be appropriate to consider any further information that becomes available. The Committee also noted that the evidence to support genetic testing was not yet sufficient.
- 6.11 The Committee considered that if non-responders to clopidogrel were indeed 30% of patients, then the supplier should provide additional information to the Committee regarding the application of a genetic test to detect these patients.

7 Bortezomib for First Line Treatment of Multiple Myeloma

Application

- 7.1 The Committee reviewed an application from Janssen-Cilag Pty Limited for the funding of bortezomib, in combination with melphalan and prednisone, as first-line treatment for patients with multiple myeloma who are unable to be treated with high dose chemotherapy.

Recommendation

- 7.2 The Committee **recommended** that bortezomib be listed in the Pharmaceutical Schedule as first-line treatment for multiple myeloma in patients unable to be treated with high dose chemotherapy and transplant. The Committee gave this recommendation a low priority.
- 7.3 The Committee further **recommended** that the application be reviewed by the Cancer Treatments Subcommittee of PTAC (CaTSoP) for advice regarding appropriate Special Authority criteria, including initial number of treatment cycles, and cost-utility analysis inputs.
- 7.4 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; (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

- 7.5 The Committee noted that it had previously considered applications for the funding of bortezomib as second and third line treatment for patients with multiple myeloma.
- 7.6 The Committee considered that current first line treatment options for multiple myeloma were dependent on the age of the patient and eligibility for stem cell transplantation. Members considered that newly diagnosed patients with multiple myeloma aged over 65 years, or younger patients with co-morbidities, would not be offered high dose chemotherapy or transplant, and that currently these patients would typically receive melphalan and prednisone (MP) as first line treatment.
- 7.7 The Committee also noted that it had recently recommended, with a high priority, that thalidomide, in combination with MP, be funded for the first line treatment of multiple myeloma in patients unable to be treated with high dose chemotherapy and transplant. Members noted that this was the same population being considered for this bortezomib application.
- 7.8 The Committee reviewed evidence provided by the supplier from one open-label randomised phase III study comparing bortezomib plus MP (BMP) with MP alone in patients with previously untreated multiple myeloma (VISTA study - San Miguel et al. NEJM 2008; 359: 906-917 and Dimopoulos et al J Clin Oncol. 2009 Dec 20;27(36):6086-93). Members also reviewed an indirect comparison of bortezomib with thalidomide, based on evidence from a number of studies comparing thalidomide plus MP with MP alone, provided by the supplier.
- 7.9 The Committee noted that the VISTA study enrolled 682 previously untreated patients ineligible for high dose chemotherapy or transplant. Patients were randomised 1:1 to receive oral melphalan 9 mg/ m² and oral prednisone 60 mg/m² given once daily on Days 1 to 4 for nine six-week cycles with or without bortezomib dosed at 1.3 mg/m² IV on days 1, 4, 8, 11, 22, 25, 29 and 32 for four cycles and days 1, 8, 22 and 29 for five cycles. Treatment was discontinued upon disease progression, unacceptable toxicity or withdrawal of patients consent.
- 7.10 The Committee noted that 344 patients were randomised to receive BMP and 338 MP. Members considered that baseline demographic characteristics were similar between the two treatment groups with the median age being 71 years for both groups, overall 23 (3%) of patients were younger than 65, with 208 (30%) aged 75 years or older.
- 7.11 The Committee noted that median time to progression, the primary endpoint of the study, was 24 months in the BMP group compared with 16.6 months in the MP group (hazard ratio, 0.48; P<0.001) and median duration of response was 19.9 months in the BMP group compared with 13.1 months in the MP group. Members also noted that bortezomib was associated with a more rapid response with median time to first response in patients treated with BMP of 1.4 months compared with 4.2 months in the MP group. Members further noted that time to subsequent therapy was longer for BMP patients compared with the control group (28.1 months vs. 19.2 months), with subsequent therapies including bortezomib, thalidomide, lenalidomide and dexamethasone.
- 7.12 The Committee noted that the rate of haematologic toxicity was similar in the two treatment groups. However, bortezomib treated patients reported a higher incidence of

peripheral neuropathy, gastrointestinal symptoms and herpes zoster infection. Members noted that herpes zoster infection was reduced in patients receiving antiviral prophylaxis.

- 7.13 The Committee noted that bortezomib was not a curative treatment; however, members considered that evidence from the VISTA study demonstrated that the addition of bortezomib to MP delayed disease progression.
- 7.14 The Committee considered that the appropriate comparator for bortezomib-MP in the first line setting was treatment with thalidomide-MP but noted that direct evidence was not available.
- 7.15 The Committee noted that based on an indirect comparison of the results from the VISTA study with other studies comparing MP with or without thalidomide the Applicant claims that bortezomib would likely be superior to thalidomide. However, the Committee noted that confounding factors, e.g. differences in study designs and patient populations including subsequent therapies, prevented meaningful comparison. Members noted that the authors of the VISTA study had themselves cautioned against comparisons with thalidomide noting that *“It would not be appropriate to compare the results of our trial with phase 3 studies of thalidomide because of confounding differences in study populations (e.g., age), the duration of therapy, the use of maintenance therapy, and especially the methodology and criteria used for definitions of response and progression.”*
- 7.16 The Committee considered that a cost-utility analysis of bortezomib compared with thalidomide should be completed. Members considered that although the toxicity profiles differed there was no clear advantage for bortezomib over thalidomide treatment and the cost of bortezomib was significantly higher than thalidomide. Members also noted that bortezomib was a hospital administered infusion whereas thalidomide was an oral tablet. Members further noted that the single use vials containing either 3.5 mg or 1 mg bortezomib will result in significant wastage of this expensive drug in the average patient who would require 2.2-2.5 mg per dose.
- 7.17 The Committee noted that in order to reduce costs the supplier had proposed that patients stop bortezomib treatment if they had not responded after four cycles of treatment. Members considered that based on the median time to first response for bortezomib treated patients in the VISTA study (4.2 months) it may be possible to reduce this to two or three cycles.

8 Docetaxel for Early Breast Cancer

Application

- 8.1 The Committee reviewed an application from the New Zealand Association of Breast Cancer Specialists – Breast Special Interest Group (BSIG) for the widening of funded access to docetaxel for the adjuvant treatment of patients with early stage breast cancer.

Recommendation

- 8.2 The Committee **recommended** that the application be declined.

- 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;* 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

- 8.4 The Committee noted that the Cancer Treatment Subcommittee (CaTSoP) had previously recommended funding of taxanes (either paclitaxel or docetaxel) for early breast cancer and that in 2006 PHARMAC widened access to paclitaxel but not docetaxel at that time because cost-utility analysis indicated that it was unlikely to be cost-effective due to its significantly higher price compared with paclitaxel. Members further noted that in 2007, funded access to docetaxel was widened to include patients with early breast cancer where docetaxel was to be given concurrently with trastuzumab for HER 2 positive disease. Members further noted that in 2007, following a price reduction for paclitaxel, the Special Authority restrictions on paclitaxel were removed, therefore, currently all patients have funded access to paclitaxel whereas only those that are HER 2 positive and receiving concurrent trastuzumab have funded access to docetaxel.
- 8.5 The Committee noted that in relation to the current funding application, which includes some new evidence, BSIG considers that docetaxel is the only taxane that has been tested in a number of specific drug combinations and many clinicians consider docetaxel their preferred taxane for adjuvant therapy of early breast cancer.
- 8.6 The Committee reviewed evidence from a number of randomised studies examining the use of various paclitaxel and/or docetaxel regimens in early and metastatic breast cancer. Members noted that a meta-analysis of studies, conducted by a PTAC member, demonstrated that treatment with either paclitaxel or docetaxel improved disease free survival (DFS) and overall survival (OS) to a similar extent when given in addition to standard chemotherapy regimens. However, members noted that the largest (n=4162) and most recent study for docetaxel did not show any overall survival or progression free survival gain from the addition of docetaxel every three weeks to standard anthracycline chemotherapy (The TACT study, Ellis et al Lancet 2009; 373: 1681–92).
- 8.7 The Committee noted that although the efficacy gains for both paclitaxel and docetaxel appeared similar the toxicity profile of these taxanes were different. Members noted across all studies the incidence of paclitaxel-associated peripheral neuropathy was approximately 17%. Members considered that the rate of docetaxel-associated peripheral neuropathy was lower however data was inconsistently reported and highly variable (range 0.2% - 25%).
- 8.8 The Committee reviewed key evidence from one study directly comparing paclitaxel with docetaxel (ECOG 11-99, Sparano et al N Engl J Med 2008; 358: 1663-71). Members noted that this was a randomised, controlled study that enrolled 4950 women with axillary lymph node-positive or high-risk, lymph node-negative breast cancer. All patients received four cycles of doxorubicin and cyclophosphamide (AC) at 3-week

intervals followed by paclitaxel or docetaxel given every three weeks for four cycles or weekly for 12 weeks.

- 8.9 The Committee noted that after a median follow-up of just over five years when compared with paclitaxel every three weeks, DFS was significantly improved in the weekly paclitaxel (HR 1.27; $p = 0.006$) and docetaxel every three weeks groups (HR 1.23; $p = 0.02$), however it was not improved in the weekly docetaxel group (HR 1.09; $p = 0.29$). Members further noted that OS was significantly improved in the group receiving weekly paclitaxel (hazard ratio, 1.32; $p = 0.01$), however it was not improved in the groups receiving docetaxel every three weeks (hazard ratio, 1.13; $p = 0.25$) or weekly docetaxel (hazard ratio, 1.02; $p = 0.80$). Members concluded that the evidence favoured weekly paclitaxel as the preferred regimen in terms of overall survival benefit and that there was no survival advantage of using docetaxel three weekly compared with paclitaxel three weekly.
- 8.10 The Committee noted that in ECOG 11-99 overall there was a 4% absolute difference in the incidence of grade 2+ neuropathy between the three weekly paclitaxel treated patients and three weekly docetaxel treated patients (20% vs. 16%). Members noted that the incidence of grade 2+ neuropathy was highest in the patients treated with weekly paclitaxel (27%). Members noted that the majority of neuropathy across treatment groups was grade 2 and the incidence of grade 3 or 4 neuropathy across groups was low (range 4 – 8%).
- 8.11 The Committee considered that overall the evidence demonstrated that the efficacy gains for paclitaxel or docetaxel were similar, however paclitaxel was associated with a modest increase in the incidence of grade 2 neuropathy. Members considered that three weekly administration of paclitaxel reduced toxicity compared with weekly paclitaxel, and there was no evidence of improved efficacy of either weekly or three weekly docetaxel compared with three weekly paclitaxel.
- 8.12 The Committee noted that there was no evidence provided regarding the duration of neuropathy, its impact on patients quality of life and/or healthcare resource use, therefore, it was difficult to quantify any health gains of docetaxel treatment compared with paclitaxel. Members noted however that the cost of docetaxel was still significantly higher than paclitaxel; therefore, members considered that any gains associated with a modest reduction in neuropathy would likely be outweighed by the increased cost of docetaxel compared with paclitaxel.

9 Bevacizumab for Metastatic Colorectal Cancer

Application

- 9.1 The Committee reviewed an application from Roche Products (NZ) Ltd for the funding of bevacizumab (Avastin) for the first line treatment of patients with metastatic colorectal cancer where the metastases are confined to the liver only.

Recommendation

- 9.2 The Committee **recommended** that bevacizumab be listed in the Pharmaceutical Schedule as first-line, neoadjuvant (Pre-surgical), treatment in patients with metastatic colorectal cancer where metastases are confined to the liver only and complete resection is planned. Members considered that bevacizumab should be funded for a maximum of 4 treatment cycles. The Committee gave this recommendation a low priority.
- 9.3 The Committee further **recommended** that the application be reviewed by the Cancer Treatments Subcommittee of PTAC (CaTSoP) for advice regarding appropriate Special Authority criteria, including the number of treatment cycles and definition of patient population, and cost-utility analysis inputs.
- 9.4 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, and (viii) The Government's priorities for health funding.*

Discussion

- 9.5 The Committee noted that colorectal cancer is a common cancer in New Zealand. Members noted that Maori and Pacific peoples were more likely to present with advanced stage disease and thus had poorer survival outcome compared with NZ Europeans. The Committee considered that this difference was mainly driven by higher patient comorbidity at presentation and poorer access to, and quality of, cancer care in Maori and Pacific peoples.
- 9.6 The Committee noted that bevacizumab is a humanised monoclonal antibody directed at vascular endothelial growth factor (VEGF-A). Members noted that bevacizumab is an add-on therapy which is given in combination with other chemotherapy agents. The Committee noted that the Cancer treatments Subcommittee of PTAC (CaTSoP) had previously reviewed an application from Roche for the funding of bevacizumab for the first-line treatment of metastatic colorectal cancer (mCRC) in 2005. Members noted that CaTSoP recommended that the application be declined, noting the high cost of bevacizumab and lack of data for its use in combination with oxaliplatin.
- 9.7 The Committee noted that the current application pertains to a subset of mCRC patients with metastases confined to the liver only. Members considered that this reflected a change in thinking in recent years regarding the prognostic significance of limited liver involvement in colorectal cancer. Members noted that unlike other cancers metastases in the liver in colorectal cancer patients are viewed as evidence of regional seeding via the hepatic portal vein, rather than systemic spread via the hepatic artery. Members noted that limited evidence suggests that radical (surgical) treatment of liver metastases improves the outcome in mCRC confined to the liver, with 5- year overall survival rates of 25-40% and 10 year OS rates of > 20%. However, members noted that the current CRC

staging systems do not yet recognise the different prognosis of metastases confined to the liver.

- 9.8 The Committee noted that evidence from a number of published studies demonstrated that chemotherapy treatment with oxaliplatin-based chemotherapy regimens improves complete surgical resection rates, thus improving progression free survival (PFS) and OS in patients with mCRC confined to the liver.
- 9.9 The Committee reviewed evidence provided by the supplier from a number of randomised, controlled studies examining the safety and efficacy of bevacizumab in combination with fluoropyrimidine and irinotecan or oxaliplatin chemotherapy regimens in mostly previously untreated mCRC patients.
- 9.10 Members also reviewed evidence from non-randomised single arm observational studies and a retrospective analysis of one randomised study examining the use of bevacizumab plus chemotherapy as neoadjuvant (pre-surgical) treatment in mCRC patients with potentially resectable liver metastases.
- 9.11 The Committee considered that there was evidence to demonstrate the addition of bevacizumab to first line chemotherapy for mCRC resulted in a modest improvement in median OS (1.4 – 7.7 months) and PFS (1.4 – 3.6 months) compared with the control groups. However, members noted that patients treated with bevacizumab treatment were at increased risk of venous thromboembolism and gastrointestinal perforation, both significant toxicities.
- 9.12 The Committee noted that evidence for the use of presurgical bevacizumab treatment was of moderate quality. The Committee noted that the only randomised comparative evidence comprised a retrospective analysis of a small number of patients enrolled in the NO16966 study (Okines et al British Journal of Cancer (2009) 101, 1033 – 1038). Members noted that this study was initially designed to compare capecitabine plus oxaliplatin (XELOX) with 5-fluorouracil plus oxaliplatin (FOLFOX4) in patients with mCRC, however it was subsequently amended to assess the addition of bevacizumab to each regimen. Members noted that of the 1401 patients randomised into NO16966, complete (R0) resection of liver metastases was achieved in only 78 patients; 44 (6.3%) bevacizumab treated patients, compared with 34 (4.9%) in the control groups, however, this difference was not statistically significant (P=0.24). Members noted that in these 78 patients 2-year OS was slightly improved in the bevacizumab treated patients, 90.9% compared with 82.3% in the control groups, but this difference was also not statistically different. Members further noted complete resection rate improved to approximately 12% overall when the analysis was confined to the subgroup of patients with metastatic disease confined to the liver at baseline, however neither resection rates nor two year OS were statistically significantly improved by the addition of bevacizumab in this subset of patients.
- 9.13 The Committee considered that given its modest efficacy and significant potential toxicity, the cost of bevacizumab was very high.
- 9.14 The Committee considered that if funded, bevacizumab would most likely be used in combination with oxaliplatin-based chemotherapy (FOLFOX or XELOX). Members noted that the supplier considered that initially bevacizumab would be used for an average of four treatment cycles in those patients where complete resection is achieved, whereas in

the remainder of non-resectable patients, treatment would be given until disease progression for an average of 18 cycles. Members considered that the cost-effectiveness of bevacizumab may be improved if its use was targeted only to those patients in whom complete resection, with curative intent, was possible. Members noted that there appeared to be little benefit of additional bevacizumab treatment in patients where complete resection was not possible.

- 9.15 The Committee considered that the amount of information provided in the suppliers application was excessive and not sufficiently focussed on evidence supporting the use of bevacizumab in the proposed subgroup.

10 Gemcitabine for Cholangiocarcinoma

Application

- 10.1 The Committee reviewed an application from the Gastrointestinal Cancer Special Interest Group of the New Zealand Association of Cancer Specialists requesting that funding of gemcitabine be widened to include treatment of patients with locally advanced or metastatic cholangiocarcinoma.

Recommendation

- 10.2 The Committee **recommended** that funding for gemcitabine in the Pharmaceutical Schedule be widened to include patients with locally advanced or metastatic cholangiocarcinoma only if cost neutral to the health sector, taking into account the costs and cost-offsets of likely substitute and subsequent therapies.
- 10.3 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; (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.*

Discussion

- 10.4 The Committee noted that the applicants used the term cholangiocarcinoma to encompass epithelial tumours of the hepatobiliary tree, including tumours of bile ducts, ampulla of Vater and gallbladder.
- 10.5 The Committee noted that cholangiocarcinoma was a relatively rare cancer with approximately 120 patients diagnosed each year in New Zealand, of which approximately 70% would present with inoperable (locally advanced or metastatic) disease. Members noted that because of its rarity, the evidence-base for cholangiocarcinoma treatments is limited.
- 10.6 The Committee considered that in New Zealand the current standard treatment for locally advanced or metastatic cholangiocarcinoma would be combination chemotherapy with

epirubicin, cisplatin and a fluoropyrimidine (infusional 5-fluorouracil or oral capecitabine) (ECF or ECX). However, members considered that the contribution of epirubicin in these treatment regimens is unclear.

- 10.7 The Committee reviewed evidence from a randomised phase II/III study of gemcitabine with or without cisplatin in patients with advanced or metastatic biliary tract cancer (ABC-02 study, Valle et al 2009). Members noted that this study was unpublished but interim data, in the form of a slide presentation, had been presented at the American Society of Clinical Oncology meeting in 2009. In this study 410 patients were randomised to receive either cisplatin (25 mg/m²) followed by gemcitabine (1000 mg/m²) on days 1 and 8 every 21 days for eight cycles, or gemcitabine alone (1000 mg/m²) on days 1, 8 and 15 every 28 days for six cycles.
- 10.8 The Committee noted that median overall survival (OS), the primary endpoint of the study, was 3.4 months longer in patients receiving cisplatin plus gemcitabine compared with gemcitabine alone. Members noted that the authors recommended cisplatin plus gemcitabine as standard of care treatment.
- 10.9 The Committee also reviewed evidence from a pooled analysis of 104, mainly non-randomised, clinical trials of various palliative chemotherapy treatments for advanced biliary tract carcinoma (Eckel and Schmid British Journal of Cancer (2007) 96, 896-902). Members noted that the authors concluded that gemcitabine on its own was not superior to fluoropyrimidines in terms of Response Rate (RR) and Tumour Control Rate (TCR), but the combination of gemcitabine with a platinum agent (e.g. cisplatin) was superior. However, members noted that although RR and TCR values were numerically higher for gemcitabine-platinum regimens compared with fluoropyrimidine-platinum regimens, the data were in fact statistically indistinguishable.
- 10.10 The Committee considered that there was a trend towards longer overall survival with combination gemcitabine plus cisplatin compared with fluoropyrimidine plus cisplatin, however, members considered that the evidence was weak and warranted further clinical research.
- 10.11 The Committee noted that the application did not discuss the role of photodynamic therapy (PDT) for locally advanced unresectable cholangiocarcinoma, members considered that PDT might represent the next best investment option for this disease.
- 10.12 The Committee considered that if funded, gemcitabine would most likely be used in combination with cisplatin for up to eight cycles, as per the ABC-02 study, rather than six cycles as the applicants suggested. Members also considered that rather than replacing current treatments, such as ECF or ECX, the use of cisplatin plus gemcitabine would simply move these treatments back in the treatment sequence, at least for some patients. Therefore, members did not consider that funding of gemcitabine would be cost saving.
- 10.13 The Committee considered that the application should be reviewed by the Cancer Treatments Subcommittee of PTAC (CaTSoP) for further advice regarding the current comparator treatments, including the value of epirubicin, the role of photodynamic therapy and the likely duration of gemcitabine treatment, should it be funded.

11 Imiquimod (Aldara) for Actinic Keratosis

Application

- 11.1 The Committee reviewed an application from Douglas Pharmaceuticals Limited for the funding of imiquimod (Aldara) on the Pharmaceutical Schedule for the treatment of actinic keratosis.

Recommendation

- 11.2 The Committee **recommended** that the application for imiquimod for the treatment of actinic keratosis be declined.
- 11.3 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

- 11.4 The Committee noted that imiquimod was an immune modifier indicated for actinic keratosis of face and scalp only in immunocompetent adults. Members noted that imiquimod was also indicated and subsidised on the Pharmaceutical Schedule for external genital warts and superficial basal cell carcinomas.
- 11.5 The Committee noted the application proposed that imiquimod would be listed on the Pharmaceutical Schedule subject to a Special Authority whereby treatment is restricted to actinic keratoses patients with a minimum of five typical lesions of the head, neck or décolleté or where other standard treatments are contraindicated or inappropriate. Members noted that the neck and the décolleté were off indication and not included in the MedSafe datasheet.
- 11.6 The Committee noted one pivotal trial (Krawtchenko et al. Br J Derm 2007;157:34-40) had been provided by the supplier relevant to imiquimod's efficacy and safety versus comparator treatments of topical 5-fluorouracil and cryotherapy. The Committee noted that this trial was a small randomised, unblinded, open label trial involving 75 patients with a one year follow up where the patient had not been subject to further or additional treatment.
- 11.7 The Committee noted that the Krawtchenko trial used a primary criterion (assumed to be the trial's end point) of test of cure (TOC) which was defined as the absence of clinically detectable actinic keratoses verified by histology. The Committee noted the results of the initial post-treatment assessment of the lesions that had been considered six weeks post-cryotherapy, four weeks post-topical 5-fluorouracil and eight weeks post-imiquimod. Members noted that for TOC there was no significant difference between imiquimod and either 5-fluorouracil or cryotherapy.
- 11.8 Members noted that cosmetic outcomes were also assessed however no significant differences at TOC were identified between any treatments. Members noted that at one year patient and investigator-determined cosmetic outcomes was deemed to be excellent in 81% treated with imiquimod compared to only 4% treated with 5-fluorouracil and cryotherapy.

- 11.9 The Committee noted that there was no safety data provided past one year and that the data provided only involved 26 patients. The Committee noted that in the Krawtchenko trial there were no serious adverse effects and that there were less irregular pigmentation and hypopigmentation in imiquimod-treated patients compared to other treatments reported. Members noted that Periodic Safety Update Report data suggests no significant safety concerns but that pharmacovigilance monitoring is needed.
- 11.10 The Committee considered that the Krawtchenko trial contained numerous limitations. Members considered that both the quality and strength of the evidence was weak and could not demonstrate that imiquimod was superior to its main comparators.
- 11.11 The Committee noted that there were discrepancies between the published Krawtchenko trial and the supplier's submission data and that the supplier had not supplied the raw clinical trial data (clinical study report). Members noted that these discrepancies had also been highlighted by an independent review of the PBAC's funding recommendation (January 2009). Members noted that the initial TOC had been performed at different time points depending upon the therapy and that this could have impacted on apparent effectiveness of treatment and did not take account of spontaneous regression of actinic keratosis. In addition, members noted that the post treatment visit was modified in the protocol for imiquimod from four weeks to the more favourable eight weeks without any explanation.
- 11.12 The Committee noted that the surface area of skin treatable with imiquimod varied considerably between different publications. The Committee noted that the Medsafe datasheet does not have a maximum surface area although the recommended maximum surface area to be treated in Australia was 25 cm². The Committee noted that this figure was derived from phase two studies where treatment of surface area >25 cm² resulted in increased systemic bioavailability of imiquimod. Members noted that there is also evidence from phase two studies that as the treatment area increases, the incidence of systemic adverse events also increases.
- 11.13 The Committee considered that treatment be limited to small areas (possibly no greater than 25 cm²) due to increasing local skin reactions and systemic adverse effects when larger areas are treated. Members noted that the Medsafe datasheet states that one sachet is enough to treat an area of 20 cm².
- 11.14 The Committee noted a supportive trial (Foley et al. 2006, unpublished) that had not been provided in the supplier's submission, which compared one year post treatment efficacy of imiquimod with cryotherapy.
- 11.15 The Committee considered, for the purposes of funding, that imiquimod has the same or similar therapeutic effect as cryotherapy and topical 5-fluorouracil. The Committee considered that a large number of patients treated with cryotherapy may convert to imiquimod as first line therapy (if funded) and therefore considered that the supplier's estimates of the patient population were underestimated.
- 11.16 The Committee noted that the supplier had not provided any pharmacoeconomic analysis. Members considered that a cost-minimisation analysis would be more appropriate as there is no evidence to suggest that imiquimod has any efficacy or safety advantages over its comparators (namely topical 5-fluorouracil and cryotherapy).

11.17 The Committee noted that the PBAC had considered imiquimod for actinic keratosis in July 2008 and rejected listing on the PBS because of uncertain evidence of effectiveness and safety versus comparator and uncertain cost-effectiveness. The Committee noted that the sponsor had sought an independent review of this decision, which had been included in the submission by PHARMAC staff, although this did not alter the PBAC's initial opinion.

11.18 The Committee recommended the following restrictions should be applied in the event that a cost-minimisation analysis was favourable versus comparator treatments and cost savings could be achieved from the inclusion of the other already funded indications:

“Treatment of clinically typical, non hyperkeratotic, non hypertrophic actinic keratosis on the face or scalp in immunocompetent adult patients when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate.”

Members further recommended consideration be given to applying the following restrictions:

“Prescriber has scope of practice that includes management of actinic keratoses.”

“Only 12 sachets per treatment course and no more than 2 treatment cycles in one year.”

12 Multiple Sclerosis Treatments

Application

17.1 The Committee reviewed a cost-utility analysis (CUA) performed by PHARMAC staff, a submission from [withheld under s9(2)(a) of the OIA] (consultant to previous applicants Bayer NZ Ltd, Sanofi Aventis NZ and Biondi Idec NZ Ltd), two additional publications provided by a neurologist, and additional material provided by PHARMAC staff, in relation to widening funded access to the multiple sclerosis (MS) treatments beta-interferon (interferon beta-1-alpha [Avonex] and interferon beta-1-beta [Betaferon]) and glatiramer acetate (Copaxone).

17.2 The Committee noted that this review continued and extended discussions relating to previous applications from the Multiple Sclerosis Society of New Zealand, the Multiple Sclerosis Treatment Assessment Committee (MSTAC) and the neurologists on the Neurological Subcommittee of PTAC relating to widening access to MS treatments, which the Committee had considered in November 2008 and August 2009.

17.3 The Committee noted that, collectively, the applicants broadly proposed three key changes to the access criteria:

- to allow treatment with a second class of MS medication after failure of treatment (as defined by current criteria) with the first class of treatment (referred to as “treatment switching”);
- to amend the entry criteria to allow earlier treatment; and

- to amend or remove the exit criteria to allow longer treatment.

Recommendation

- 17.4 The Committee again **recommended** that all applications to amend the entry criteria for funded access to MS treatments be declined, on the basis of lack of strong evidence and likely poor cost-effectiveness.
- 17.5 The Committee reiterated its previous **recommendation** (made in November 2008) that the criteria for access to MS treatments 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 are met. The Committee again assigned a medium priority rating to this recommendation.
- 17.6 The Committee also reiterated its previous **recommendation** to alter the exit criteria for MS treatments as previously described (in November 2008). However, the Committee altered the priority of this recommendation from medium (as prioritised in November 2008) to low, based on lack of evidence of effectiveness and poor cost-effectiveness of MS treatments.
- 17.7 The Committee also reiterated its previous **recommendation** that the application to remove the exit criteria entirely be declined.
- 17.8 The Decision Criteria particularly relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

Treatment switching

- 17.9 The Committee reviewed the evidence in the [withheld under s9(2)(a) of the OIA] submission in support of treatment switching and relapse rates. The Committee noted that it had previously reviewed all three cited studies (Caon et al. Eur J Neurol 2006;13:471–4 ; Carra et al. Eur J Neurol 2008;15:386–93; Zwibel HL. Acta Neurol Scand 2006;113:378-86) in November 2008.
- 17.10 The Committee considered that, overall, these three studies suggest relapse rates before treatment switching of between 0.89 and 1.5, and after treatment switching of between 0.15 and 0.53. The Committee considered that there is a high risk of bias in these estimates (i.e. likely to be overestimates) because of non-randomized allocation to treatment, no control groups, unmasked observation of outcomes and likely incomplete data. The Committee noted that these figures are of the same order of magnitude as in a publication reviewed by the Committee in August 2009 (Gajofatto et al. Multiple Sclerosis 2009;15:50-8) which the Committee had previously considered to have 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.

- 17.11 The Committee considered that magnitude of the bias may be addressed by the reported relapse rate in the PRISMS trial, a placebo controlled randomised controlled trial (RCT) of beta-interferon (PRISMS Study Group. Lancet 1998;352:1498–504). In this trial, which measured patients for a median of two years, the annualised relapse rate prior to treatment was 1.5 and in the placebo group it was 1.28 per year in the two year trial period, but in the beta-interferon groups it was between 0.87 and 0.91 per year in the trial period. Thus, the relapse rates reported after treatment switching in the uncontrolled cohort studies were about half those reported in a randomised trial.
- 17.12 Overall, the Committee considered that the evidence supporting a reduction in relapse rates following treatment switching was weak and the estimates of a reduction in relapse rates of around two thirds was likely to be biased upwards, overstating true effectiveness. The Committee considered that the most appropriate relapse rates to use in modelling are from the RCTs: around 0.9 per year in treatment groups and 1.28 for no treatment.

Disease regression with short to medium-term improvement in EDSS scores provided by MS treatments

- 17.13 The Committee noted the assertion in the [withheld under s9(2)(a) of the OIA] submission that MS treatments can be associated with short-term disease improvement with regression of EDSS states, with an average of 10%–20% of patients in placebo arms and 20%–30% of patients in treatment arms improving in Expanded Disability Status Scale (EDSS) score in clinical trials. The Committee noted that no clinical trial citation details were provided to support this assertion.
- 17.14 The Committee noted that in the Cochrane review of beta-interferon in relapsing-remitting MS (Rice et al. Cochrane Database Syst Rev. 2001;(4):CD002002) the mean difference in EDSS for the two studies that measured this at two years was –0.025 (95% CI –0.46 to –0.05), but that the authors of the review had cautioned that this difference was of questionable clinical importance and would be difficult to measure in clinical practice because of the nature of the EDSS scale.
- 17.15 The Committee noted that the Cochrane review did not consider the number of patients who improve, but if non-progression is considered then about 80% of those on IFNB did not progress at about two years and around 71% of those on placebo. The Committee found it difficult to reconcile these figures with the [withheld under s9(2)(a) of the OIA] review comment of 20-30% and 10-20% respectively; the PRISMS publication did not clearly state how many participants improved.
- 17.16 The Committee considered that using the New Zealand funded MS patient data to support a claim of disease improvement from treatment had multiple possible confounding factors, including the short-term fluctuations in MS, a number of different clinicians reporting EDSS scores, and presumably different starting times with reference to exacerbations of the therapy.

- 17.17 Overall, the Committee considered that there was no strong evidence supporting a short to medium-term improvement in EDSS score from MS treatments, and remained unconvinced by the evidence that had been presented.

Early vs. late treatment

- 17.18 The Committee reviewed the evidence in the [withheld under s9(2)(a) of the OIA] submission in support of the effectiveness of earlier treatment in MS. The Committee considered that the evidence provided was weak, consisting of a narrative style review (Tintore. J Neurol 2008;255(Suppl 1):37-43) and one cohort study (Coppola et al. Eur J Neurol 2006;13:1014-21) with a high risk of bias because of the large number of drop-outs, unmasked assessment of outcomes, non-randomised allocation of treatment, and the mixture of relapsing-remitting and relapsing-progressive MS patients. In addition, the Coppola publication presented multiple subgroup analyses without evidence that interaction terms were tested or adjustment made for multiple statistical testing.
- 17.19 The Committee also reviewed the two publications provided by the neurologist (Trojano et al. Ann Neurol 2009;66:513-20; Trojano et al. Int MS J 2009;16:90-97), which related to the efficacy of earlier treatment . The first paper (Ann Neurol 2009) was a prospective cohort study of 2,570 patients with MS treated in 15 Italian MS centres with beta-interferon and followed for seven years; the second was a description of propensity scoring (Int MS J 2009). In the cohort study, 310 (12.6%) patients had treatment started within one year of onset of symptoms, with a median EDSS 1.5 (range 1.0 to 5.5); the remaining 2,260 patients, with treatment starting at a median EDSS 2.0 (range 1.0 to 5.5), were the comparator group. The risk of having an EDSS progression of 1 or progressing to EDSS 4 was estimated after adjusting for factors which may have lead to receiving early versus late therapy (propensity scoring, described in the second publication) in an attempt to reduce bias. At five years, the adjusted risk for progression to EDSS 4 was 14% for the early and 20% for the late treatment group, and for progression by 1 EDSS point 22% in the early and 36% in the late treatment group. The Committee considered that the cohort study provided moderate evidence of an effect of initiating treatment within one year of onset of symptoms, with evidence of a modest effect at five years on progression.
- 17.20 The Committee considered that available evidence, from a 2008 Cochrane review (Clerico et al. Cochrane Database Syst Rev 2008; Apr 16;(2):CD005278) and the PreCISe trial (Comi et al. Lancet 2009;374:1503-11), suggested that treatment of early MS reduces recurrence rate at two years; however, there appears to be no evidence demonstrating that this benefit is maintained in the longer term.

UK MS Risk Sharing Scheme

- 17.21 The Committee reviewed two publications relating to outcomes of patients with MS treated in the UK (Pickin et al BMC Neurology 2009;9:206-13; Boggild et al. BMJ 2009;339:b4677).
- 17.22 The Pickin paper, included in the [withheld under s9(2)(a) of the OIA] submission, was a simple description of the monitoring of uncontrolled outcomes of patients treated in the UK from 2002, which was part of a risk-sharing scheme between the National Health Service (NHS) and the suppliers of MS treatments for a 10-year monitoring program under which the price of the medication would be adjusted to achieve a cost per QALY

of £36,000. This paper was cited in the [withheld under s9(2)(a) of the OIA] submission as the main evidence of beta-interferon being associated with short-term disease improvement with regression of EDSS states (see paragraph 17.23 above).

- 17.23 The Boggild paper, sourced separately to the [withheld under s9(2)(a) of the OIA] submission, further reported the utility changes observed at two years in the scheme, together with EDSS changes for the MS risk-sharing cohort compared with expected figures based on an Ontario MS data set and the results of the RCTs. The paper reported that 5,583 patients registered in the scheme, 3,686 were eligible for analysis and had some follow up data, and 2,609 were still receiving original treatment at two years. Of the 3,686 patients eligible for analysis, the mean EDSS at baseline was 3.05. For those with two year data (n=2,901), the mean EDSS at baseline was 2.68 and the mean EDSS at two year follow-up was 3.24, with a mean deterioration of 0.56. By way of comparison, the Rice et al 2001 Cochrane review had reported the change from baseline EDSS at two years for the treatment arms for the two trials reporting this outcome measure as 0.24 and -0.07, and for the control arms of 0.48 and 0.21. In other words, the mean change in EDSS from baseline in the observed UK cohort was worse than the mean change from baseline in the control (standard treatment) arms in the two RCTs that reported this outcome. In the Boggild paper, utility differences were predicted (on the basis of EDSS) at two years to be 0.0254 without treatment and 0.0158 with treatment (a difference of -0.0096). The utility change of the actual cohort group based on their EDSS was 0.0266, and hence the difference from predicted with treatment was -0.0108. The Committee noted that the ratio of the two differences was 1.125, equating to the 113% deviation reported in the Boggild paper, i.e. in the actual cohort the treatment arm fared worse than anticipated.
- 17.24 The Committee noted that the authors of the Boggild paper had postulated several reasons for this observation. However, the Committee considered that, on balance, the results of the UK risk-sharing scheme at two years strongly suggested that the results of the RCTs of beta-interferon and of non-experimental studies of effectiveness may have been biased towards overstating true efficacy and therefore unduly favouring treatment. The Committee therefore considered that in the sensitivity analyses for CUA, less optimistic assumptions should be given more weight. The Committee considered that the risk of bias in the UK risk-sharing analysis seemed high, with a large amount of missing data, but it is unclear in which direction the bias lay. Members also noted a commentary that had been submitted to the BMJ (McCabe et al) which opined that the Boggild analysis may still have overestimated the effectiveness of interferon and glatiramer treatments.

Effectiveness of glatiramer

- 17.25 The Committee considered that evidence supporting the effectiveness of glatiramer in MS (eg in Munari et al. Cochrane Database Syst Rev 2004;(1):CD004678) did not appear to be as robust as that supporting beta-interferon; however, the Committee considered that on the basis of the available evidence it was reasonable to assume that the effect size of treatment with glatiramer was of the same order of magnitude as for beta-interferon, and that this assumption could be incorporated into PHARMAC's CUA modelling.

Baseline relapse rates affecting disease progression

- 17.26 The Committee reviewed the information provided in the [withheld under s9(2)(a) of the OIA] submission regarding the adaptation of the ScHaRR model to a New Zealand setting. This comprised four papers relating to baseline relapse rates and their associations with EDSS disease progression.
- 17.27 The first paper (Manriolo et al. J Neurol 2008; 255:1023-31) was a retrospective study of patients with MS presenting to a single clinic in Italy. Of 348 consecutive patients with MS, 111 had MS for at least 10 years; a final group of 64 were studied, of whom 26 had an EDSS of 4 or more after 10 years and 38 had a score of 3 or less. A very large number of variables were chosen to explore probability of having a low versus high score (about 30 in the first table of the paper). Tables 2 and 4 of the paper state that time to relapse of greater than two years was not associated with high or low EDSS score although it is not clear when these relapses occurred. In table 3, 14 variables and two outcomes (EDSS scores of 3 or 4) were analysed by proportional hazards; it is not clear what the response is in this table e.g. reaching an EDSS score of 3 versus not. Less frequent relapses were associated with a lower risk of attaining an EDSS score of 3 or more. The Committee considered this paper had a number of important flaws, being is a retrospective analysis of a secondary care setting, with large numbers of patients not considered, and a statistical analysis highly prone to Type I error.
- 17.28 The second paper (Weinshenker et al. Brain 1989;112:1419-28) described predictive prognostic values derived from the London Ontario prospective descriptive study of a cohort of patients with MS seen in clinic from 1979 to 1984. The paper detailed EDSS scores and the frequency of attacks in the first two years of onset of MS. Figure 1A of the paper described survival curves stratified by attack frequency in the first two years of MS versus developing an EDSS score of 6 or greater. The separation of curves was statistically significant but no hazard ratios were given. Reading from the graph the median time for EDSS 6 was eight years when there had been four or more attacks in the first two years, versus 15 years for two to four attacks initially, and 20 years for less than two attacks. The ratios for medians were 8:20 (0.4) and 15:20 (0.75). The Committee considered this to be an older study without modern imaging that suggests increased attack frequency, particularly four or more attacks in two years, is associated with a greater chance of progression to EDSS than fewer than two attacks a year.
- 17.29 The third paper (Langer-Gould et al. Arch Neurol 2006;63:1686-1691) was a systematic review of predictors of long-term disability. Meta-analysis of the effect of early relapse frequency could not be attempted because of heterogeneity of study design and failure in nearly all studies to report confidence intervals for hazard ratios. The forest plot for the effect of early relapse was presented in Figure K. The authors' comments on early relapse frequency were that "In contrast [to shorter interval between first and second attack], a higher relapse frequency was not always associated with a poor prognosis and, within studies, the magnitude of the effect was influenced by the definition of disability." The authors were not able to give a quantitative assessment of the risk. The Committee considered this systematic review to be of high quality, and noted that it could only find some inconsistent evidence that increased early attack rates are associated with worse prognosis.
- 17.30 The fourth paper (Ebers. J Neurol 2005;252 (Supplement 5):S15-S20.) is a narrative style review of results from the Ontario MS dataset described in the above Weinshenker paper. The Committee noted that the reference by the [withheld under s9(2)(a) of the OIA] submission to the association between early relapse rates and prognosis is to this paper.

- 17.31 The Committee considered that the two cited studies (Manriolo; Weinshenker) provided poor quality or no independent evidence. The systematic review of prognostic factors (Langer-Gould) represented high quality evidence, but as its authors noted although it seems likely that increased early relapse rates are associated with more rapid development of disability the study reports are inadequate to quantify this risk. The Committee also considered that the data from the Ontario cohort (Weinshenker; Ebers) represented moderate evidence of the association but no hazard ratios had been presented to quantify this risk. The Committee also noted that the Langer-Gould systematic review did not include the data from the London Ontario cohort, as it did not meet its eligibility criteria as the data did not distinguish between primary progressive and relapsing-remitting MS.
- 17.32 In addition to the material cited by [withheld under s9(2)(a) of the OIA], the Committee was aware of three other papers that did not support a clear relationship between relapse rates and disease progression (McDonald N Engl J Med 2000;343:1486-1487; Kremenchutzky et al. Brain 2006;129:584-94; Vikusic & Confavreux Curr Opin Neurol 2007;20:269-74.). It was noted that in the Kremenchutzky paper, which updated the London Ontario cohort data (the Weinshenker and Ebers papers in paragraphs 17.28 and 17.30 above), the authors concluded that their survival analyses demonstrated that the progressive course is independent of relapses either preceding the onset of relapse-free progression or subsequent to it.
- 17.33 The Committee noted that the analysis of the UK risk sharing scheme (Boggild BMJ 2009, paragraph 17.23 above) reported that the two year annualised relapse rate was 1.45 before treatment and 0.58 after treatment. In the PRISMS trial the annualised relapse rate moved from 1.5 to 0.9 in the treatment group and 1.5 to 1.28 in the placebo group, a risk reduction for relapse of 0.7.
- 17.34 The Committee considered that the evidence that a reduction in relapse rates leads to a marked reduction in disability progression to be inconsistent and weak, as illustrated by the small EDSS reductions for active treatment versus control in the RCTs.

Quality of life at EDSS levels

- 17.35 The Committee reviewed the evidence provided in the [withheld under s9(2)(a) of the OIA] submission describing quality of life experienced at various EDSS levels relating to relapse risk and the effects of delaying treatment. The Committee noted that the Naci 2009 conference presentation citation has now been published (Naci et al. J Med Econ 2010;13:78-89). The Committee noted that this publication was a systematic review of the literature (not a meta-analysis) and no quantitative statements are made about the association between EDSS and health utilities. The comment had been made in the text of the [withheld under s9(2)(a) of the OIA] review that 'patients lose over a third of their health related quality of life between EDSS states 0 and 3. Between states 3 and 6 they lose only one tenth.' This appears to have been made by estimating the health utilities for these health states from 'Figure 1' of the conference presentation paper. Although the full published paper did not provide summary estimates for the EDSS/utilities association, the paper did provide sufficient tabulated data to calculate approximate summary study participant number-weighted utility scores for EDSS states (assuming that each study had the same proportion of participants in each EDSS state), albeit data from three studies were omitted from the published tables.

- 17.36 Using the Naci et al publication, the Committee calculated summary associations, using only the studies that were included in Figure 1 of the full publication, for EDSS state 0 of 0.9 (weighted mean utility) from two studies; EDSS '0-1' of 0.86 (8 studies); EDSS 1 of 0.82 (2 studies); EDSS 2 of 0.72 (10 studies); EDSS 3 of 0.61 (11 studies); EDSS 4 of 0.62 (11 studies); EDSS 5 of 0.58 (11 studies); EDSS 6 of 0.49 (11 studies); EDSS 6.5 of 0.46 (10 studies); EDSS 7 of 0.36 (11 studies); EDSS '8-9' of 0.07 (8 studies); EDSS 8 of -0.03 (2 studies); and EDSS 9 of -0.18 (2 studies)..
- 17.37 The Committee noted that the differences in utility between different EDSS health states depend on which boundary points are used. For example the difference between '0-1' and '3' is 0.25; and between '3' and '6' is 0.12.
- 17.38 The Committee considered the Naci et al systematic review was of good quality and summarised the association between EDSS states and health utilities in Europe and the UK. Weaknesses of the systematic review were that it did not describe what is meant by EDSS states '0-1' and '8-9', did not explain the omission of three studies from the published summary plots of utility values by EDSS scores, and did not describe why EDSS states '0-1' and '8-9' were handled the way they were in Figure 1 of the full publication, and did not present confidence intervals for these associations which may be important if differing numbers of participants contributed to the different EDSS health states (e.g. few patients in EDSS health states less than 1 means these confidence intervals will be wide).
- 17.39 The Committee noted that although utilities in the Naci et al systematic review were consistent across the studies presented, there would be some uncertainty about the application to NZ populations.

Quality of life and relapses

- 17.40 The Committee considered the information in the [withheld under s9(2)(a) of the OIA] submission relating to the impact of relapses on patients' quality of life. This comprised nine papers.
- 17.41 The first paper (Parkin et al. J Neurol Neurosurg Psych 2000;68:114-49) described a retrospective notes review of 102 patients attending a UK neurology service. Details of how the sample was obtained were not given but the relapse patients had to have attended hospital and so may have had worse relapses than similar patients in randomised trials of IFNB. 40 patients had experienced a relapse in the last six months and 62 who had not. EDSS was not routinely collected as part of the case notes and was estimated retrospectively by the consultant neurologist managing the patients. EQ-5D quality of life scores were measured by postal questionnaires, and differed according to relapse/remission status: those in the remission group kept a diary of six weeks, whereas those in the relapse group were asked to retrospectively rate how they were currently and at the worst part of their relapse. There was no information readily available that specified either the time period before the questionnaire that patients had experienced their relapse, or how long the symptoms associated with the relapse lasted. 50 of the 102 patients had face to face interviews from which utilities were assigned based on EQ-5D. The difference in utilities was based on the mean utilities of each of the remission and the relapse groups, presumably at the time of worst effect of the relapse.

- 17.42 In the Parkin paper, EDSS scores could be applied to 89 of the 102 patients. The summarised results were that 33/89 (37%) had an EDSS of 0-3, 32/89 (36%) of 4-5, and 24/89 (27%) of 6+. The mean utilities at EDSS 3, 4, 5, 6, and 7 were 0.71, 0.66, 0.52, 0.49 and 0.35, respectively; the Committee noted that these were similar to the summarised results from Naci et al 2010. The paper had stated that the mean utility taking account of EQ-5D in remission was 0.604 and in relapse 0.136, difference 0.468. This appeared not to refer to those participants who had a relapse (i.e., the before and after values in specific patients) but was comparing all those in the state of remission with all those in the state of relapse.
- 17.43 The Committee considered that the Parkin paper had several weaknesses; it is unclear as to the patient population the study represents, the EDSS scores were applied retrospectively (and are, therefore, subject to recall bias), data were missing for about 15% of patients, differences between relapses and remissions were based on different sets of patients (not the same patients experiencing both states), and there is no mention in the paper of how long the effect of relapses lasted. The Committee considered that the figure of 0.468 utility loss was upwardly biased, i.e. higher than it actually was.
- 17.44 The second paper (Nuitjen et al. *Value in Health* 2002;5:44-54) described a cost-effectiveness analysis of beta-interferon in MS. The paper states that the utility loss with relapse is 0.5 and this lasts for one month. However, the reference for these figures was to a Health Technology Assessment (HTA) from 1998 by Parkin et al (Parkin D et al. *Health Tech Assess* 1998;2(4)), where the patient group used for those data had 102 subjects and seems to be identical to that described in the Parkin et al 2000 paper described in paragraphs 17.40-17.43 above. The HTA report used a range of relapse utility losses of between 0.25 and 0.75 and duration of relapse of between two and six weeks in its sensitivity analysis. The figures of 0.5 utility loss and 30 day duration appear to come from the figures used in the HTA sensitivity analyses for evaluation of two years of treatment with beta-interferon or glatiramer. The Committee therefore considered this paper cited utility loss and duration for relapse that were used as part of a sensitivity analysis in another paper.
- 17.45 The third paper (Bose et al. *J Med Econ* 2001;4:207-19) described an analysis of glatiramer for MS. The utility loss of 0.5 per relapse was said to be taken from the Parkin 1998 HTA (referred to in the above paragraph). The duration of utility loss of two months was taken from another publication (Liu et al. *J Neurol Neurosurg Psych* 1998;64:726-9), which appeared to be a concept paper suggesting an alternative way of measuring outcome in MS trials; the authors had stated "natural history studies on cohorts with early multiple sclerosis have shown that up to 24% of relapses last more than three months" and referred to papers published in 1952 and 1973. The Committee considered that under the circumstances the two month duration appeared to be relatively arbitrary.
- 17.46 The fourth paper (Chilcott et al. *BMJ* 2003;326:522-8) was a summary of the School of Health and Related Research, Sheffield University, UK (ScHaRR) report to the National Institute of Clinical Excellence (NICE) (Tappenden et al. Final report to the National Institute of Clinical Excellence [ScHaRR Report]). In neither paper were the utility changes with relapse or the duration of relapse stated by drug and trial, as these were described as 'commercial in confidence'. In a summary statement of the Chilcott paper it was stated that transition from EDSS 0 to 3 was associated with a 30% reduction in quality of life, the same magnitude as from EDSS 3 to 7. However, the base utility and

whether this reduction is absolute or relative was not stated. The data were based on the reports of randomised controlled trials of treatment for relapsing-remitting MS.

- 17.47 The Committee noted that the figures quoted in the [withheld under s9(2)(a) of the OIA] submission of 0.22 (standard deviation (SD) 0.089) utility loss for 42 (SD 20) days were reported in the SchARR Report (Tappenden) as the parameterisation of the distribution for a Bayesian analysis of uncertainty associated with the analysis and were presumably the point estimates from all the five data sets for the RCTs combined, but it was unclear if this was for the placebo arms of the trials.
- 17.48 The Committee noted that the figure of 0.08 loss of utility with 42 days duration in the SchARR material was not referenced apart from 'early Kobelt data'. The Committee noted that Kobelt had published extensively in this area and without further information it is not possible to be certain of the source material for this statement. The Kobelt paper cited in the Chilcott paper [<http://swopec.hhs.se/hastef/papers/hastef0398.pdf>] was published as an on-line document in August 2000 by SWOPEC, Stockholm School of Economics. The data was based on written or in-person responses to disease and QoL questionnaires after attendance at one of three clinics in the UK. Utilities were derived from the EQ-5D. 619 patients were recruited but there was missing data for a moderate proportion of the patients. Regarding relapse and utility loss, the closest the Committee could find to utility for relapse in the last month versus those with no relapses in the last 12 months was in Table 10, which categorised relapses as within the last 1-2 months or within the last year. Additionally there was an apparent error in the table as the utilities for those with and without relapses at one year, 0.542 versus 0.430, appear to be transposed the wrong way around (relapse is associated with a higher utility). For the 1-2 month figure the utility with/without relapse appeared to be the correct way around, 0.457 and 0.497. The Committee questioned whether the utility loss associated with relapse in the [withheld under s9(2)(a) of the OIA] paper may have been the difference between 0.54 and 0.46, i.e. 0.08. The Committee could not find any indication of mean duration of relapse in this Kobelt publication.
- 17.49 The Committee noted that it was not possible to assess the quality of these estimates of utility loss due to relapse or duration, as the original material was not cited in the [withheld under s9(2)(a) of the OIA] report. However, the Committee thought it was probable that the SchARR point estimates of 0.22 utility loss and a duration of 42 days were robust estimates although their source material was not available.
- 17.50 The fifth paper (Orme et al. Value in Health 2007;10:54-60) was based on a postal survey of 13,000 people on the UK to the MS Trust (UK) database. 2000 survey instruments (16%) were suitable for analysis. 29% of the analysed group reported a relapse in the last three months and on multivariate analysis had a utility 0.071 less than those not reporting a relapse. The 90 days cited by the [withheld under s9(2)(a) of the OIA] review presumably referred to the three month figure for those that reported a relapse in the last three months. The Committee considered there was a very high risk of bias due to non-response. In addition it was not clear for any individual respondent the change in utility with a relapse or how long the relapse lasted for.
- 17.51 The sixth paper was a working paper published on the Stockholm School of Economics website (Kobelt et al. 2004 <http://econpapers.repec.org/paper/hhshastef/default2.htm>). This described a postal survey of a random sample of 4000 patients from 24,000 patients on a consortium group of MS treatment centres in the US. All the patients had

received treatment with a disease modifying agent. Around 1900 valid survey forms were received. 29% reported a relapse in the previous three months, and 14% weren't sure or didn't reply to this question. Those without a relapse in the last three months (1087/1909, 57%) had a mean utility of 0.742, and those with a relapse in the last three months (544/1909, 29%) 0.648, a difference of 0.094.

- 17.52 The Committee considered there was a very high risk of bias due to non-responses, the three month time period (relating to relapse in the last three months), comparing those with relapse with those without, and no objective definition of relapse.
- 17.53 The seventh paper (Henriksson et al. Eur J Neurol 2001;8:27-35) was a postal survey of patients with MS from a single neurology centre in Stockholm, Sweden. 413/543 (76%) responded. EDSS level '0-3' had a utility value of 0.68, '3.5-6.0' had a value of 0.52, and '6.5+' had a value of 0.17. The utility for those experiencing a relapse (time period not specified) was 0.0635 lower than those in remission. The Committee considered there was a high risk of bias due to non-response, was unsure how the time to relapse could be established, noted there was no objective definition of relapse, and was unsure which groups were being compared for relapse utility.
- 17.54 The eighth paper (Berg J et al. Eur J Health Econ 2006;7 (Supplement 2);S75-85) was a postal survey of those belonging to a national association for those with neurological disease. Of 2100 forms posted to those registered as interested in MS, 1339 (64%) responded. 18% reported a relapse in the last three months but 27% were unsure or didn't answer. The utility loss associated for those with relapse was 0.088 for those with EDSS scores less than 5, and 0.029 for those greater or equal to 5. Insufficient summary data was given to estimate the overall relapse rate. The Committee was unsure what the sample frame was, and noted likely high non-response bias, no objective definition of a relapse, sub-group analysis of utility loss, and unclear time frames.
- 17.55 The ninth paper (Grima et al. Multiple Sclerosis 2000;6:91-98) involved interviews with patients presenting to two neurology centres for review. The paper was unclear on the number of MS patients who presented over the study period. 153 patients in remission and 42 in relapse were interviewed. Those in remission who had a relapse in the last six months (44/153, 28.8%) were also asked about the relapse. EDSS level 1 had a utility score of 0.83, EDSS 2 a score of 0.84, EDSS 3 a score of 0.71, EDSS 4 a score of 0.71, EDSS 5 a score of 0.62, and EDSS 6 as score of 0.59. Patients with EDSS levels higher than 6 were excluded. The Committee noted that loss of utility associated with a relapse was presented in a figure stratified by EDSS score and was difficult to read. The Committee considered there was a high risk of bias in estimates which were not, in any case, presented in a format that could be reliably estimated.
- 17.56 Overall, the Committee considered that most of the cited evidence was of poor quality and the interpretation in the [withheld under s9(2)(a) of the OIA] submission was not robust. The Committee noted that in only one of the citations was material about utility loss associated with a relapse gathered prospectively and a reliable time course for the duration of the relapse specified; this was in the summary estimates for all RCTs combined in the SchARR Report, as specified in the parameterisation of the uncertainty for these; namely, a mean utility loss of 0.22 with an SD suggested of 0.089 and mean duration of relapse of 42 days with an SD suggested of 20 days. The Committee considered that the risk of bias in the other cited papers was very high and in none of the other citations was the time course for the relapse actually measured.

17.57 The Committee noted that if plus or minus one standard deviations were chosen as the parameter to use for relapse-related inputs in the sensitivity analyses, covering the central 65% of the spread of these measurements based on the uncertainty estimates from the SchHARR Report, this would suggest a range for utility loss of 0.13 to 0.31 and a range of duration of 22 to 62 days. Using a 0.22 utility loss for 42/365 days would equate to 0.0253 QALY loss, which was less than that suggested as the mean estimate in the [withheld under s9(2)(a) of the OIA] submission (0.034). The range by the above suggestion is 0.13 for 22/365 days (0.0078) to 0.31 for 62/365 (0.053).

Cost-effectiveness of treating patients with early disease progression

17.58 The Committee reviewed the information provided in the [withheld under s9(2)(a) of the OIA] submission relating to the cost-effectiveness of treating patients with early disease progression versus treating later (as per the current access criteria). The Committee considered that the quality of the contributory evidence cited (Chilcott; Tappenden; Bose; Langer-Gould) was moderate to high. The Committee noted that the comprehensive SchHARR Report gave a mean duration of 9.2 years for the time in EDSS state 0-1 (Tappenden, page 41), but that this had been derived for the purposes of SchHARR's economic model and that the source mean times for the DSS0 and DSS1, derived from empirical 25-year follow-up data, were 6.96 and 13.25 years respectively (Tappenden pages 7, 40). The Committee considered that the data from Naci et al 2010 (using the weighted mean utilities calculated in paragraph 17.36 above) supported average losses in utility of ~~[0.83]~~ **0.10** per unit for EDSS0-3 and 0.04 per unit for EDSS3-6, with a resulting ~~[2:1]~~ **2.5:1** ratio for the rate of utility lost for lower vs. higher EDSS scores (i.e. earlier vs. later).² For EDSS progression, using the SchHARR Report empirical natural history data for RRMS and SPMS (which excluded PPMS and benign MS), the expected ratio was 3.4:1 ((6.96+13.25+6.56)/3=8.9 years vs. 2.6 years); using the SchHARR Report adjustments to meet its modelling requirements, the expected ratio was 2.2:1 ((3.08+6.16+6.56)/3=5.3 years vs. 2.6 years).

17.59 The Committee noted that [withheld under s9(2)(a) of the OIA] submission referred to patient factors associated with poor prognosis from the Langer-Gould review (sphincter symptoms at onset, incomplete recovery from first attack, and a short interval between the first and second attack) and that having patients at EDSS of 0 alongside these factors would lead to a cost-effective use of therapy. However, members considered that no evidence was presented to support treatment of patients based on these prognostic factors, and in the Committee's view it appeared highly unlikely that patients could be in EDSS 0 and simultaneously have one of those factors.

17.60 The Committee noted the provisional CUA modelling conducted by PHARMAC staff to date suggested that early treatment (patients starting at EDSS levels 0 to 3) appeared to be less cost-effective than later treatment (EDSS levels 3-5, being the current access criteria). Further details of the provisional CUA modelling to date, and important caveats, are in paragraphs 17.63-17.64 below. The Committee also noted that such CUA modelling, which routinely uses long time horizons and estimates all consequent costs

² The Committee revised its view of the utility value for EDSS0-3 in paragraph 17.58 (and the consequent ratio for the rate of utility lost for lower vs. higher EDSS scores (i.e. earlier vs. later)) at an email meeting on 26 August to 6 September 2010, and agreed to amend the utility value and the consequent ratio (each substitution being a deletion in ~~strike through~~ followed by an addition in **bold**).

and benefits of treatment versus standard care, was the approach that would adequately manage any varying effects from discounting or other health sector costs over time.

- 17.61 The Committee considered that an appropriate economic analysis in the form of a CUA of early treatment (EDSS of 0) needed to be performed, using the above calculations of mean utility in different EDSS states. The Committee considered that the SchARR mean times in each state are appropriate to use in the analysis, but care is needed as to handling of the state '0-1'.

Costs of widening access by allowing switching to alternative MS treatments or by relaxing exit criteria

- 17.62 The Committee considered the [withheld under s9(2)(a) of the OIA] submission provided no evidence regarding the costs of widening access by allowing switching to alternative MS treatments or by relaxing exit criteria, aside from using the New Zealand MS Treatment Access Scheme data.

Provisional cost-utility analysis results

- 17.63 The Committee noted the provisional results to date presented by PHARMAC staff from the updated CUA modelling so far. This modelling had used revised disease progression estimates that included time spent in the various EDSS states and associated costs and quality of life effects (and assumed exiting after a one point EDSS decline or no relapse decline), and was heavily contingent on the Committees' advice regarding clinical assumptions and inputs. This initial analysis had suggested base case results in the broad range of \$50,000 to \$100,000 per QALY depending on the baseline EDSS levels at which treatment started, with early treatment appearing to be less cost-effective than later treatment (see paragraph 17.60 above). In addition, with this initial analysis, similar to previous models, the results were strongly sensitive to disease progression, with treatment being more cost-effective with faster disease progression. For example, starting at EDSS 0 (stopping treatment at 1) was strongly sensitive to the duration to which patients remain in EDSS 0 before transiting to EDSS 1 (where delaying disease progression for EDSS 0 appreciably increased the cost per QALY).

- 17.64 The Committee noted that such results were highly provisional and might change appreciably as a result of amending clinical assumptions in the model structure and inputs.

Assumptions recommended for use in the updated cost utility

- 17.65 For relapse rates leading to reductions in disease progression, the Committee reiterated its view that the evidence that reducing relapse rates leads to a marked reduction in disability progression was inconsistent and weak, and did not recommend changes to the PHARMAC CUA model.

- 17.66 The Committee also stated that it was important to note that in a real-life cohort of the UK risk sharing trial the actively treated patients appeared to progress faster than the placebo groups in the RCTs, and that a less optimistic sensitivity analysis was therefore appropriate.

- 17.67 For relapses themselves, the Committee considered that the SchARR mean values for 0.22 utility loss and 42 day average time seemed appropriate, but as discussed in the paragraph above it may be better to use less optimistic figures as it seemed unlikely that treatment will be better than this, i.e. lower risk reduction of relapses, less utility loss and for a shorter time period.
- 17.68 For disease regression, the Committee reiterated that this should not be considered in the PHARMAC CUA models, as while there may be relatively short term improvements in individual patients the average over the medium term is for deterioration.
- 17.69 For health state utility values, the Committee reiterated its recommendation based on the weighted means from the Naci publication. The Committee also stressed the need for care with utilities for the '0-1' category of the EDSS.
- 17.70 For the costs for patients in the varying EDSS states used in the economic model, the Committee considered it appropriate to use the costs from the SchARR model and convert these to NZ dollars.

Concluding observations

- 17.71 The Committee noted the results of two double-blind, double dummy randomised clinical trials of fingolimod in relapsing-remitting MS (Cohen et al. New Engl J Med 2010;362:402-15; Kappos et al. New Engl J Med 2010;362:387-401), both with over 1,000 participants, in which there appeared to be no difference in annualised relapse rates between the beta-interferon arm of one study and the placebo arm of the other study.
- 17.72 Overall, the Committee considered that the evidence for the effectiveness of beta-interferon and glatiramer in any MS disease state was weak.
- 17.73 The Committee noted that its conclusions differed to those of the Neurological Subcommittee and the Multiple Sclerosis Treatments Advisory Committee and considered it would like a face-to-face meeting with these two groups.

13 Olanzapine Depot Injection (Zyprexa Relprevv)

Application

- 13.1 The Committee reviewed a cost-utility analysis (CUA) and budget impact analysis (BIA) performed by PHARMAC staff in relation to an application by Eli Lilly for funding of olanzapine depot injection (Zyprexa Relprevv) for the treatment of patients with schizophrenia and related disorders who have tried but been unable to comply with treatment using oral antipsychotic agents and who have been admitted to hospital or treated in respite care, or intensive outpatient or home-based treatment, for 30 days or more in the last 12 months.

Recommendation

- 13.2 The Committee **recommended** that olanzapine depot injection be funded, subject to Special Authority restrictions, for the treatment of patients with schizophrenia and related disorders who have tried but been unable to comply with treatment using oral antipsychotic agents and who have been admitted to hospital or treated in respite care, or intensive outpatient or home-based treatment, for 30 days or more in the last 12 months, only if it was no cost to the Pharmaceutical Budget over the cost of risperidone depot injection (Risperdal Consta). The Committee further **recommended** that if olanzapine depot injection was funded at a higher price than risperidone depot injection it would be reasonable to add an additional requirement for patients to have first tried risperidone depot injection.
- 13.3 The Decision Criteria particularly relevant to these recommendations 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, (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

- 13.4 The Committee noted that the application for funding of olanzapine depot injection had previously been reviewed by PTAC in May 2009 and November 2009 and by the Mental Health Subcommittee of PTAC in July 2009, and that the Committee had until now deferred making a recommendation pending review of a CUA and BIA performed by PHARMAC staff.
- 13.5 The Committee noted that the result of the CUA was that olanzapine depot injection was dominated by the comparator treatments (olanzapine tablets and wafers; and risperidone depot injection), because it was more expensive and was associated with lower quality adjusted life year (QALY) gains overall.
- 13.6 The Committee noted that there was a subset of patients for whom olanzapine depot injection would currently be relatively cost-effective, being those who had received a sub-optimal therapeutic response from risperidone depot injection. However, the Committee noted that under the criteria proposed by the supplier this patient group would constitute a small proportion of patients that could receive olanzapine depot injection. The Committee noted that the cost per QALY for patients who were non-compliant on olanzapine tablets/wafers would be over \$500,000, and that this figure would likely be substantially higher with generic entry into the tablet market following patent expiry in 2011.
- 13.7 The Committee considered that the assumptions in the CUA model were reasonable given the available evidence. Members noted the uncertainty of the persistence of weight gain after patients cease treatment, and noted that PHARMAC staff had included this in the sensitivity analysis in the CUA.

14 Anxiolytics, Sedatives and Hypnotics – Review of Dispensing Restrictions

Application

- 14.1 The Committee considered a request from PHARMAC staff to review the dispensing restrictions that currently apply to the sedatives, hypnotics and anxiolytics.

Recommendation

- 14.2 The Committee **recommended** that the “month restriction” be removed from lorazepam, midazolam, nitrazepam, temazepam, triazolam, zopiclone, alprazolam, buspirone, diazepam, lorazepam and oxazepam, and gave a high priority to this recommendation.
- 14.3 The Decision Criteria particularly relevant to this recommendation are: *(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, (vii) The direct cost to health service users.*

Discussion

- 14.4 The Committee noted that currently most forms and presentations of the sedatives, hypnotics and anxiolytics listed in the Pharmaceutical Schedule (lorazepam, midazolam, nitrazepam, temazepam, triazolam, zopiclone, alprazolam, buspirone, diazepam, lorazepam and oxazepam) were funded for a maximum of one month per prescription, meaning that repeat dispensings from the same prescription are not subsidised.
- 14.5 The Committee noted that there are no legal restrictions preventing repeats of these medications from being prescribed or dispensed; however, under the current funding rules patients would have to pay for repeat dispensings themselves, or obtain a new prescription in order to receive additional funding.
- 14.6 The Committee noted that prescribing guidelines generally recommend short courses of treatment only for these pharmaceuticals, mainly because of limited evidence for long-term benefit and the risks of tolerance, dependence, abuse, diversion and overdose.
- 14.7 However, the Committee acknowledged that the reality of clinical practice is such that there are many people who are prescribed these treatments for periods of longer than one month, most of whom have stable usage and do not divert the medications. The Committee noted that there were many instances where this may be clinically appropriate, for example in patients with chronic spasticity, chronic severe anxiety or post-traumatic stress disorder.
- 14.8 The Committee considered that it would be reasonable for such patients to receive funding for repeat dispensings. The Committee noted that such patients could receive more than a months’ funding anyway, if they obtained additional prescriptions from their

clinicians. The Committee considered that this situation placed an unnecessary burden on prescribers and patients.

- 14.9 The Committee considered that it was important that no more than one month of these pharmaceuticals be dispensed at a time for safety reasons, and for this reason the Committee was not supportive of replacing the “month restriction” with a funding rule that allow stat (all-at-once) dispensing for prescriptions with more than a month’s worth of the pharmaceutical.
- 14.10 The Committee noted that removing the “month restriction” from the relevant pharmaceuticals, without adding any other funding rule, would result in the medications being subject to the default “monthly dispensing” rule, meaning that repeats would be subsidised but only one month could be dispensed at a time. The Committee considered that such a restriction would be appropriate.

15 Naltrexone Hydrochloride Special Authority

Application

- 15.1 The Committee considered a request from two addiction specialists to review the Special Authority restriction applying to naltrexone hydrochloride relating to the requirement for the applicant to be working in a community Alcohol and Drug Service contracted to one of the 21 District Health Boards or accredited against the New Zealand Alcohol and Other Drug Sector Standard or the National Mental Health Sector Standard.

Recommendation

- 15.2 The Committee **recommended** that the following change be made to the Special Authority criteria applying to naltrexone hydrochloride (addition in bold):

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

All of the following:

1 Patient is currently enrolled in a recognised comprehensive treatment programme for alcohol dependence; and

2 Applicant works in **or with** a community Alcohol and Drug Service contracted to one of the 21 District Health Boards or accredited against the New Zealand Alcohol and Other Drug Sector Standard or the National Mental Health Sector Standard.

Renewal from any medical practitioner. Approvals valid for 3 months for applications meeting the following criteria:

Both:

1 Compliance with the medication (prescriber determined); and

2 Any of the following:

2.1 Patient is still unstable and requires further treatment; or

2.2 Patient achieved significant improvement but requires further treatment; or

2.3 Patient is well controlled but requires maintenance therapy.

The patient must have had no more than 1 prior approval in the last 12 months.

Discussion

- 15.3 The Committee noted that community Alcohol and Drug Services in some areas appeared to be overburdened, such that there was a limited number of specialists available to assess patients with alcohol addiction and that some specialists (including the applicants) felt that their time could be better directed to other patients.
- 15.4 While appreciative of the resourcing issue, the Committee noted that the intent of the relevant criterion (criterion 2 in the initial application) was to ensure that patients were appropriately reviewed and enrolled in a suitable treatment programme prior to commencing treatment with naltrexone. The Committee considered that the clinicians most qualified to assess such patients would be those who worked in a community Alcohol and Drug Service and, as such, considered that the criterion was appropriate.
- 15.5 The Committee noted that many community Alcohol and Drug Services employed/contracted part-time medical officers (typically with a background in general practice) to provide general medical services and medical triage to patients referred to their service. The Committee considered that these clinicians should be able to apply for naltrexone Special Authorities and considered that a minor word change (as per the recommendation) should capture such prescribers.

16 Adalimumab Weekly Dosing and Second-line Treatments for Rheumatoid Arthritis following Adalimumab Failure

Application

- 16.1 The Committee considered a request from PHARMAC staff to review the Special Authority for adalimumab; specifically, around the possibility of excluding weekly dosing of adalimumab for maintenance treatment in the funded indications, and further restricting the renewal criteria for Crohn's disease. The Committee also reviewed draft cost-effectiveness advice to DHB hospitals on the use of infliximab, abatacept or rituximab for the second-line treatment of rheumatoid arthritis following failure of adalimumab prepared by PHARMAC staff.

Recommendation

- 16.2 The Committee **recommended** that 40 mg weekly dosing be specifically excluded from the adalimumab Special Authority renewal criteria for all funded indications, with the exception of patients with rheumatoid arthritis not taking concomitant methotrexate who have received inadequate benefit from fortnightly administration. The Committee further **recommended** that the adalimumab Special Authority renewal criteria for Crohn's disease be amended to specify a level of response that must be met in order for patients to continue accessing funded treatment.

Discussion

- 16.3 The Committee noted that PHARMAC staff had received requests for clarification from clinicians wanting to know if adalimumab would be funded if given at a dose of 40 mg per

week for patients with Crohn's disease, and that one clinician had provided some information from Abbott on this topic for PHARMAC's review.

- 16.4 The Committee noted that the adalimumab Medsafe datasheet specifies that adalimumab be administered at a maintenance dose of 40 mg per fortnight for all funded indications except rheumatoid arthritis, where the datasheet states "some patients not taking concomitant methotrexate may derive additional benefit from increasing the dosing frequency of adalimumab to 40 mg every week."
- 16.5 The Committee noted there was very little evidence available assessing the efficacy of weekly dosing with adalimumab in Crohn's disease. It considered that the available evidence, including from the CHARM trial (Colombel et al. *Gastroenterology* 2007;132:52-65, Colombel et al. *Am J Gastroenterol* 2009;104:1170-79), the CLASSIC II trial (Sandborn et al. *Gut* 2007;56:1232-9) and a retrospective single-centre review (Swaminath et al. *Aliment Pharmacol Ther* 2009;29:273-8), did not support the efficacy of 40 mg weekly dosing over 40 mg fortnightly dosing of adalimumab in the maintenance treatment of Crohn's disease, including in non-responders to 40 mg fortnightly dosing or in patients with disease "flare". The Committee noted that the cost-effectiveness of adalimumab in Crohn's disease would be considerably worsened if adalimumab was administered weekly instead of fortnightly.
- 16.6 The Committee noted that it was not aware of any evidence to support an increase in the dosing schedule from 40 mg fortnightly to 40 mg weekly for any funded indication.
- 16.7 For these reasons, the Committee considered that 40 mg weekly dosing should be specifically excluded from the renewal criteria for all funded indications, with the exception of patients with rheumatoid arthritis not taking concomitant methotrexate who have received inadequate benefit from fortnightly administration.
- 16.8 The Committee noted that the current renewal criteria for the use of adalimumab in Crohn's disease require that "the treatment remains appropriate and the patient is benefiting from treatment." The Committee considered that the renewal criteria for Crohn's disease were too vague, and should be strengthened to specify a level of response required to be met in order to obtain ongoing funding, similar to the criteria in Australia or Canada.
- 16.9 The Committee considered that the draft cost-effectiveness advice to DHBs was well worded and did not have any specific comments or suggestions in relation to this advice.