

PTAC meeting held 10 & 11 November 2011

(minutes for web publishing)

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

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

PTAC may:

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

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

- (i) enable PHARMAC to carry on, without prejudice or disadvantage, negotiations (including commercial and industrial negotiations) (section 9(2)(j)).

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1 Matters Arising

Varenicline (Champix) for smoking cessation

- 1.1 The Committee noted that it had reviewed recent safety data for varenicline (Champix) relating to neuropsychiatric and cardiovascular adverse events at its August 2011 meeting and had recommended that varenicline safety be reviewed again by PTAC following the September 2011 review of varenicline by Medsafe's Medicines Adverse Reactions Committee (MARC).
- 1.2 The Committee noted the minutes from MARC's 8 September 2011 meeting at which MARC had reviewed the cardiovascular safety information for varenicline. The Committee noted that MARC considers that although cardiovascular related safety concerns have been raised in association with varenicline, a causal relationship has yet to be demonstrated and that the information does not alter the benefit-risk balance for varenicline. The Committee noted that MARC had recommended that the varenicline Medsafe datasheet be updated to include information about reports of cardiovascular related adverse events associated with the use of varenicline, which was being actioned by the supplier (Pfizer). The Committee considered that this was appropriate.
- 1.3 The Committee reviewed additional information in relation to the neuropsychiatric side effects of varenicline, including a recent Drug Safety Communication from the US Food and Drug Administration entitled "Safety review update of Chantix (varenicline) and risk of neuropsychiatric adverse events," a recent publication of an analysis of varenicline post-marketing reports (Moore et al, PLoS One 2011;6(11):e27016) and Pfizer's media response, and a report of a cohort study of varenicline and suicidal behaviour from the UK (Gunnell et al, BMJ 2009;339:b3805).
- 1.4 The Committee noted that the clinical trials of varenicline had not shown an increase in neuropsychiatric events; however, the Committee considered that the trials may not have been adequately powered to detect such events and noted that the patients selected for inclusion in the trials did not necessarily reflect the range of patients seen in clinical practice.
- 1.5 The Committee noted that there were ongoing trials of varenicline in patients with depression and schizophrenia, which it understood were being conducted to further investigate the neuropsychiatric effects of varenicline. However, the Committee noted that the post-marketing reports for varenicline had identified suicidal behaviour in patients with no history of mental illness, so the trials would not necessarily be useful in determining the neuropsychiatric risk in the general population.
- 1.6 The Committee reiterated its previous view that the adverse psychiatric events associated with varenicline are real, and noted that it continued to have significant concerns around the clinical risks of varenicline given the available safety data in relation to these events.

2 Subcommittee minutes

2.1 Cancer Treatments Subcommittee – 26 August 2011

2.1.1 The Committee did not agree with CaTSoP's recommendation to remove the Special Authority from short acting octreotide preparations. Members considered that whilst there would be limited increased use in oncology indications removal of the Special Authority restriction applying to short acting octreotide would likely result in significant increased use in gastrointestinal indications such as high output stomas. The Committee **recommended** that PHARMAC seek further advice from the Gastrointestinal Subcommittee on the removal of the Special Authority from short acting octreotide

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

3 Enzyme Replacement Therapies

Application

3.1 The Committee considered an application from PHARMAC staff that sought advice on whether to list six Enzyme Replacement Therapies (ERTs) for five lysosomal storage diseases on the Pharmaceutical Schedule.

Recommendations

3.2 The Committee **recommended** that the proposal to fund agalsidase alpha (Replagal) for the treatment of Fabry disease be declined.

3.3 The Committee **recommended** that the proposal to fund agalsidase beta (Fabrazyme) for the treatment of Fabry disease be declined.

3.4 The Committee **recommended** that the proposal to fund laronidase (Aldurazyme) for the treatment of Mucopolysaccharidosis I (Hurler, Hurler-Scheie and Scheie disease) be declined.

3.5 The Committee **recommended** that the proposal to fund idursulfase (Elaprase) for the treatment of Mucopolysaccharidosis II (Hunter disease) be declined.

3.6 The Committee **recommended** that the proposal to fund galsulfase (Naglazyme) for the treatment of Mucopolysaccharidosis VI (Maroteaux-Lamy disease) be declined.

3.7 The Committee **recommended** that the proposal to fund alglucosidase alpha (Myozyme) for the treatment of Pompe disease (infantile, juvenile and adult-onset) be declined.

3.8 The Decision Criteria particularly relevant to all 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 and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.

Discussion

- 3.9 The Committee considered an application from PHARMAC staff that sought advice on the funding of various Enzyme Replacement Therapies (ERTs) generated following receipt of responses to a Request for Information (RFI) issued by PHARMAC on the 9 May 2011. The RFI sought evidence to support: the causal association between improved surrogate markers and clinical outcomes that ERTs reduce mortality, further information regarding optimum doses and dosing protocols, and proposed pricing for New Zealand supply. The Committee noted responses and all evidence provided by pharmaceutical suppliers, the National Metabolic Service, NZ Organisation for Rare Disorders, Mayo Clinic and two patients.
- 3.10 The Committee noted that it had previously reviewed the funding of six ERTs at its February 2009 meeting, and again, specifically the funding of alglucosidase alpha for adult-onset Pompe disease at its February 2011 meeting. The Committee noted that it was aware of funding applications for ERT treatments for individual patients received through the Exceptional Circumstances scheme.
- 3.11 The Committee considered that in general ERTs comprised high cost, highly specialised medicines and noted that a recent review of the process of evaluating the funding of high cost, highly specialised medicines, which is published online at www.beehive.govt.nz, recommended that 'prioritisation and funding decisions concerning high-cost, highly specialised medicines continue to be made in the same way as such decisions for other medicines'.
- 3.12 The Committee noted the severe nature of these lysosomal storage diseases. It was noted that even if the evidence of effectiveness were to improve, at the current costs of ERT treatment it would be challenging to make their cost effectiveness argument. The committee considered that at the present time best supportive care should be the treatment option.
- 3.13 The Committee's discussion of various disease settings and ERTs are detailed separately below:

Fabry disease

Agalsidase beta

- 3.14 The Committee considered evidence submitted by Genzyme, the supplier of agalsidase beta (Fabrazyme), in relation to the optimum dosing regimens. The Committee considered that the standard dose in trials of agalsidase beta (Fabrazyme) is 1mg/kg/fortnight, although members noted that one study (Lubanda et al 2009; 11:256-264) used this dose for 6 months then 0.3mg/kg/fortnight thereafter. Members noted that in this two year trial 70-90% of patients maintained their initial clearance of

globotriaosylceramide (GL-3) from the kidney. The Committee considered this data suggested that dose reduction following an initial treatment phase may offer similar efficacy and would significantly reduce the cost of treatment compared with standard dosing.

- 3.15 The Committee considered evidence provided by Genzyme regarding the effect of agalsidase beta treatment on renal outcomes. The Committee considered a multicentre, randomised, double-blind, placebo-controlled study published by Banikazemi et al. (*Ann Intern Med* 2007; 146:77-86) designed to assess the effectiveness of agalsidase beta compared with placebo on time to clinically significant progression of renal, cardiac, cerebrovascular disease and/or death in 82 patients with advanced Fabry disease. Members noted that patients were randomised (2:1) to receive treatment with either 1 mg/kg/fortnight of agalsidase beta or placebo for up to 35 months. The Committee noted that although there appeared to be a trend in favour of agalsidase beta there was no statistically significant difference in the rate of clinical progression between the two treatment groups for any efficacy endpoint over the duration of the study suggesting that agalsidase beta treatment may take years before significant clinical benefits are seen, if any. Other than this trial, the Committee considered that there was little new evidence to support any effect of agalsidase beta on renal outcomes.
- 3.16 The Committee also considered evidence regarding the effect of agalsidase beta on cardiac disease. The Committee considered a five month, double-blind, randomised, placebo controlled trial (Thurberg et al. *Circulation* 2009;119:2561-2567) followed by an open-label extension study which demonstrated that agalsidase beta was effective in clearing globotriaosylceramide (GL-3) from capillary endothelial cells of the heart and this effect was sustained for up to five years. However, the Committee noted that in this study no effect was seen on GL-3 deposition in cardiomyocytes and there was no evidence of improved cardiac function, or other clinically meaningful end points such as reduction of myocardial infarction or cardiac death.
- 3.17 The Committee also considered evidence from three small, single arm, open label, studies (Imbriaco et al. *Heart* 2009;95: 1103-7, Weidemann et al. *Circulation* 2009; 119: 524-529, Collin et al. *Euro J Cardio Prev & Rehab* 2011), all published since its last review which showed a reduction in left ventricular hypertrophy, reduction in aortic stiffness and improvement in baroreflex function with agalsidase-beta treatment. Overall, the Committee considered that, despite evidence of effect of agalsidase beta on some cardiac measures, there was no evidence to support its effect on clinically meaningful endpoints.
- 3.18 The Committee also considered evidence from a single arm, open label, study published by Watt et al. (*Genet Med* 2010;12 703-712) regarding effect of agalsidase beta treatment on quality of life in 130 patients treated with agalsidase beta. Members considered that agalsidase beta improved quality of life measures over two years of treatment, however, these improvements were not sustained beyond three years of treatment.

Agalsidase alpha

- 3.19 The Committee considered evidence submitted by Shire, the supplier of agalsidase alpha (Replagal). The Committee noted that the standard dose of agalsidase alpha in

all trials was 0.2mg/kg/fortnight (five times lower than the dose of agalsidase beta). The Committee considered that agalsidase alpha and agalsidase beta were functionally indistinguishable and that no convincing evidence had been provided demonstrating any significant difference between the two enzymes in their effect on surrogate markers and clinical end points, despite agalsidase beta at 1mg/kg/fortnight producing a higher percentage of antibodies than agalsidase alpha at 0.2mg/kg/fortnight (Vedder et al. *Mol Genet Metab* 2008; 94:319-25; reviewed by PTAC previously).

- 3.20 The Committee considered evidence supplied in support of the clinical effect of agalsidase alpha treatment comprising two studies that used data obtained from the Fabry Outcome Survey observational (FOS) database. The Committee reviewed evidence from a single arm observational study (Mehta et al. *Lancet* 2009; 374:1986-96) of 181 patients enrolled in FOS who were treated with agalsidase alpha for 5 years. Members noted that in patients with baseline cardiac hypertrophy, treatment with agalsidase alpha significantly reduced left ventricular mass (LVM) and increased midwall fractional shortening (MFS). However, in patients without baseline hypertrophy LVM and MFS remained stable. Members noted that patient quality of life and pain were improved significantly, and the rate of decline in glomerular filtration rate (GFR) was less than that seen in historical controls. The Committee also considered a 3 year analysis of renal function outcomes in 165 patients enrolled in the FOS (Ferriozzi et al. *Am J Nephrol* 2009; 353-361). Members noted that the authors found a significant increase in serum creatinine, decreased GFR and increased proteinuria, but reported that the rate of decline in renal function was less than historical controls. A baseline proteinuria of >500mg/24 hours and, to a lesser extent hypertension predicted accelerated loss of renal function. The Committee noted that in both studies, concomitant use of ACE-inhibitors and angiotensin II receptor blockers were common and may have influenced outcomes.
- 3.21 The Committee noted that there were no new safety concerns published in the FOS annual report from 2010. The database contained 1,903 patients, of whom 1,120 had been treated with agalsidase alpha. Safety statistics reported showing 18% of patients had serious adverse events, 9% had infusion related reactions (IRRs) and 5% died. Overall, the Committee considered that the evidence for agalsidase alpha was weak and its effect on clinically meaningful endpoints was unclear.

Migalastat

- 3.22 The Committee considered a submission from Amicus, the supplier of the pharmacological chaperone migalastat (Amigal), which targets misfolded endogenous enzymes, as a result of specific mutations, in patients with Fabry disease. The Committee considered evidence from a non-randomised, single arm, extension study (Schiffman et al. *J Peds* 2011) which examined the long-term safety, tolerability and renal function of migalastat treatment in patients with Fabry Disease. Members noted that 26 patients completed the primary 12-24 week treatment period, and 23 patients completed 24-84 week initial extension period and were then enrolled in a separate long term extension study. Members noted that the authors reported that migalastat reduced levels of kidney globotriaosylceramide compared with baseline in patients with Fabry disease with responsive mutations of alpha-galactosidase A. Members also noted that glomerular filtration rate remained stable and some subjects with responsive mutations observed reduced proteinuria compared with baseline. The Committee noted that these effects were maintained out to 3-4 years and are comparable to results

reported for ERT. The Committee noted that migalastat is currently in Phase III development and is not registered in New Zealand.

Meta-analysis

- 3.23 The Committee considered evidence from a Cochrane review (El Dib et al. Cochrane Database of Systematic Reviews 2010; Issue 5) of a meta-analysis five randomised controlled trials of ERT (agalsidase alpha or beta) in Fabry disease. The Committee noted that it had previously reviewed evidence from four of these studies (Banikazemi et al. *Ann Int Med* 2007;146:77-86, Eng et al. *New Eng J Med* 2001; 345:9-16, Hughes et al. *Heart* 2008;94: 153-8 and Schiffman et al. *JAMA* 2001; 285:2743-9) with the fifth being a small study comprising 15 patients (Bierer et al. *J Inh Metab Dis* 2006;29:572-9). The Committee noted that the authors reported a non-statistically significant improvement in serial cardiopulmonary exercise testing following 18 months treatment with agalsidase beta compared with placebo. Members noted, and agreed with, the authors conclusion that “five small, poor quality randomised controlled trials provide no robust evidence for use of either agalsidase alpha or beta to treat Anderson-Fabry disease”.
- 3.24 The Committee considered evidence from a review article submitted by the National Metabolic Service (NMS) (Lidove et al. *Genet Med* 2010;12:668-679) of the clinical efficacy of ERT in Fabry disease, however, members noted that the end points considered were all surrogates and considered their relevance to clinical outcomes was questionable.

General Discussion – Fabry disease

- 3.25 The Committee considered that agalsidase alpha and agalsidase beta are expensive treatments with limited evidence for clinical benefit and poor cost-effectiveness. The Committee considered that whilst evidence demonstrates that agalsidase (beta and alpha) clears GL-3 from plasma and organs, and that this occurs in all ages, genders and different ethnicities, this has not been shown to translate to improved organ function or delayed clinical progression in patients with Fabry disease. The Committee considered that many years of ERT treatment may be necessary before meaningful clinical benefits, if any, would be seen in patients with Fabry disease.
- 3.26 The Committee considered that overall the evidence provided in the various submissions was poor in quality and weak to moderate in strength. The Committee noted that the evidence reviewed to date suggests that the most beneficial use of ERT is likely to be early in the course of disease, potentially in childhood, before the onset of proteinuria, left ventricular hypertrophy or other organ involvement and that treatment of established disease may not be clinically beneficial.
- 3.27 The Committee considered that there remained concerns around serious adverse effects, infusion related reactions and neutralising antibody formation with agalsidase. The Committee considered it to be still only a hypothesis that the higher dose of 1 mg/kg agalsidase beta may saturate existing antibodies overcoming the negative effect of neutralising antibody formation leading to greater effectiveness of the therapy (Vedder et al. *Mol Genet Metab* 2008; 94:319-25). The Committee considered that there are important unanswered questions about the optimum treatment for reversal,

maintenance and prevention of Fabry's disease, optimum dosing protocols, including the frequency of infusions, and the long term risks and benefits of ERT treatment.

Mucopolysaccharidosis I (Hurler, Hurler-Scheie and Scheie syndrome)

- 3.28 The Committee considered a submission from Genzyme, the supplier of laronidase (Aldurazyme). Members noted that the recommended dose of laronidase in patients with mucopolysaccharidosis I (MPS I) is 100U/kg weekly by IV infusion. The Committee further noted that this dose was established by Giugliana et al. (Mol Genet Metab 2009; 96:13-19) in a dose-optimisation study and that this dose provided the best benefit to risk ratio. The Committee noted that there is no data on the effect of dose reductions for laronidase once a patient is stabilised.
- 3.29 The Committee noted that the supplier did not provide any relevant new evidence for consideration. The Committee considered evidence from 2010 MPS I Registry Report (www.mpsiregistry.com) however, members noted that this did not contain any information on the ongoing clinical benefits of laronidase for MPS I patients. The Committee considered that although the supplier claimed that surrogate markers in clinical trials of 6 minute walk test (6MWT) and forced vital capacity (FVC) were "increasingly understood as predictors of survival in diseases such as MPS I" no published reference was provided to support this view.
- 3.30 The Committee also considered evidence from a case series observational study (Wynn et al. J Pediatr 2009; 154:135-9) of outcomes of stem cell transplantation in 18 consecutive patients with MPS I Hurler syndrome under two years old. Patients received weekly IV infusions of laronidase at 100U/Kg for 12 or more weeks pre-transplantation and until donor cell engraftment post-transplantation. The survival rate after first transplantation was 100%, however, 4 patients developed graft failure, all of whom required a second transplant and one a third. Of these 4 patients, two died and two successfully grafted the second time, thus overall, survival was 89%. Members noted that the authors considered that historically, 15% children with MPS I Hurler syndrome do not survive transplantation and engraftment is unsuccessful in 44% of cases. The authors attributed the higher engraftment and survival results seen in the study as being due to the accumulated effect of full-intensity conditioning regimens, well matched donors, individualisation of GVHD prophylaxis and good supportive care. The authors' conclusion that the benefit of laronidase is linked to improvement in a patient's pre-transplantation condition and thus their tolerance of such intensive therapy was noted.
- 3.31 The Committee considered a submission from the National Metabolic Service (NMS) suggesting that laronidase could be targeted for patients with MPS I pre- and post-transplant. The Committee considered the evidence submitted by the NMS which comprised case studies reporting variable improvement in some patients in various end points: including exercise tolerance, respiratory function, joint pain and range of motion, sleep disorder, mobility, quality of life and mood.
- 3.32 The Committee considered that there was little new data provided since its previous review in 2009 and the strength and quality of evidence reviewed was weak. The Committee considered that laronidase may not improve organ systems when irreversible changes have already developed and it is ineffective in neurological

disease. The Committee considered that virtually all patients develop IgG neutralising antibodies and more than half exhibit infusion related reactions. The Committee considered that use in the pre and post transplant setting requires further evidence and noted that such new evidence could be reviewed by them in the future.

- 3.33 Overall, the Committee considered that laronidase has a consistent but small effect on study end points out to 3.5 years and possibly 6 years although members noted the studies were small and considered that the effect may not be clinically meaningful. However, the Committee considered that the long term benefit of laronidase, and its effect on morbidity and mortality, is unknown at this time and requires longer term studies.

Mucopolysaccharidosis II (MPS II) – Hunter’s disease

- 3.34 The Committee considered a submission from Genzyme, the supplier of idursulfase (Elaprase) for the treatment of Hunter’s disease. The Committee noted that idursulfase is administered by weekly IV infusion at a recommended dose of 0.5mg/Kg over 3 hours to treat non-neurological manifestations of the disease.
- 3.35 The Committee considered three studies published since its last review which assessed the efficacy and safety of idursulfase. The Committee considered evidence from a prospective observational cohort study of idursulfase in 94 patients with MPS II, published after its last review in 2009 (Muenzer J et al. *Genet Med* 2011; 13:95-101). Members noted that all patients received IV idursulfase at a dose of 0.5 mg/kg weekly for 2 years. Members noted that no change from baseline in the percent predicted forced vital capacity was seen, but absolute forced vital capacity demonstrated sustained improvement and was increased by a mean of 25.1% by the end of the study ($p<0.05$). Members further noted statistically significant improvements in 6-minute walking test distance were observed at most time points with the greatest absolute improvement seen at 20 months (42m), but at 3 years the gain, although statistically significant ($p<0.01$), was only 25m ($p<0.01$). Members noted that mean liver and spleen volumes remained stable throughout the 2-year extension study. The Committee noted that infusion-related adverse events occurred in 53% of patients and peaked at month 3 of treatment and declined thereafter and that neutralising IgG antibodies were detected in 23% of patients and seemed to attenuate the improvement in pulmonary function.
- 3.36 The Committee considered evidence from a 12 month retrospective observational cohort study (Okuyama et al. *Molecular Genetics and Metabolism* 2010; 99:18–25) in 10 Japanese adults aged 21-53 years who received weekly idursulfase. Members noted that treatment with idursulfase resulted in significant reductions compared with baseline in urinary glycosaminoglycan, liver and spleen volume, but non-statistically significant reductions in forced vital capacity, the 6 minute walk test, left ventricular mass index, left ventricular ejection fraction and joint range of motion.
- 3.37 The Committee considered evidence from a study published by Muenzer J et al. (*Genet Med* 2011; 13:102-9), which used the Hunter Outcome Survey to carry out a retrospective analysis of open-labelled treated patients and included 124 patients younger than 6 years old, and 287 patients older than 6 years. Members noted that treatment with idursulfase resulted in significant reductions in urinary glycosaminoglycans and liver size. Members noted that IgG neutralising antibodies

were detected in 53.5% and 42.8% of patients younger and older than 6 years respectively. The Committee noted that the study authors concluded that long term observation would be required to determine whether early initiation could prevent progression of clinical disease.

- 3.38 The Committee considered evidence from by Glamuzina et al. (J Inherit Metab Dis 2011; 34:749-54) provided in the NMS submission, which retrospectively compared the populations enrolled in two studies (Muenzer et al. Genet Med 8:465–473, Muenzer et al. Mol Genet Metab 2007 90:329–337) to a treatment population from Great Ormond Street Hospital, London. The authors concluded that the end points used in the trials may not be applicable to everyday practice and could not be used as an indicator of treatment efficacy in the clinical setting. The Committee noted that the weaknesses of this study were its retrospective design and that the populations differed particularly in age, height and CNS disease. The Committee noted that these weaknesses mitigate the authors' conclusions.
- 3.39 The Committee noted that the supplier of idursulfase agreed with international guidelines that patients with neurological disease should not be treated, and made reference to a recent paper which demonstrated that in this population brain MRI features worsen despite ERT treatment (Manara et al. J Inherit Metab Dis 2011, 34:763 – 780).
- 3.40 Overall, the Committee considered that the quality and strength of the evidence provided for the idursulfase for MPS II was weak. The Committee considered that the most improvement, if any, occurred in the first 12-18 months of treatment with idursulfase, with little improvement thereafter. The Committee considered that infusion related reactions can be serious and life threatening. The Committee considered that the long term safety and efficacy of idursulfase remained unknown at this time and longer term studies were required.

Mucopolysaccharidosis VI (Maroteaux-Lamy disease)

- 3.41 The Committee noted that the supplier of galsulfase (Naglazyme) for MPS VI did not submit any relevant new information. The Committee considered the submission by the NMS in which it suggested that patients with severe MPS VI would probably be best managed by bone marrow transplantation, mild cases do not warrant ERT, and moderate cases should be assessed on a case by case basis. The Committee considered that the evidence previously reviewed was weak and showed no significant effect of galsulfase on respiratory, cardiac or musculoskeletal function, and has no effect on central nervous system disease.

Pompe disease

- 3.42 The Committee considered evidence submitted by Genzyme, the supplier of alglucosidase alpha (Myozyme) to support its use in the treatment of infantile, juvenile and adult-onset Pompe disease.

Infantile-onset Pompe disease

- 3.43 The Committee noted that it has previously reviewed evidence for infantile-onset Pompe disease in 2009. The Committee considered evidence from a retrospective

observational cohort study by Chakrapani et al. (J Inherit Metab Dis 2010;33:747-50) which reported the outcome of all patients with infantile-onset Pompe disease treated in the United Kingdom since the availability of alglucosidase alpha. The Committee noted that a total of 20 infants were treated from 2000 to 2009 with median ages at diagnosis and treatment of 5.75 months and 6.5 months respectively and the median duration of treatment was 31 months. The Committee noted that overall ventilator free survival was 35%, while 35% died at a median age of 10 months and 30% were alive but ventilator dependent. The Committee considered that overall the outcomes in this study were worse than in the pivotal clinical trials, possibly due to later diagnosis and patients being at the severe end of the clinical spectrum.

- 3.44 The Committee also considered evidence from a retrospective observational cohort study by Chien et al. (Pediatrics 2009;124:1116-25) which reported outcomes for six patients with infantile Pompe disease, five of whom were screened at birth, diagnosed with a rapidly progressive form of Pompe disease and treated soon after diagnosis (12-34 days old). Members noted that the sixth patient was started on treatment at 14 months of age because of progressive muscle weakness. The Committee noted that the five screened infants who had early cardiac involvement demonstrated normalisation of cardiac size and muscle pathology with normal physical growth and age-appropriate gains in motor development and survival was significantly improved compared with those in an untreated reference historical cohort ($p=0.001$). The Committee noted that the sixth patient who started on treatment at 14 months of age due to progressive muscle weakness also achieved normal motor development with treatment. The Committee noted that all patients were cross-reactive immunologic material (CRIM) positive.
- 3.45 The Committee noted that CRIM status may affect treatment outcomes in patients with infantile-onset Pompe disease. Members noted that the NMS agreed with this view and also noted that the response to ERT treatment is very variable. The Committee noted that to identify CRIM status in New Zealand takes approximately two months but the Adelaide LSD lab may be able to provide results in two weeks. However, members noted that the rationale to test for CRIM status at birth is weaker, in the absence of a funded treatment.
- 3.46 Overall, the Committee considered that the evidence suggests that early diagnosis and treatment, preferably before 6 months of age may be important in determining longer term outcomes and that alglucosidase alpha treatment may improve respiratory and motor function and lifespan in some patients, however the long term effect on morbidity and survival is unknown.

Juvenile and adult-onset Pompe disease

- 3.47 The Committee noted that it had reviewed the evidence to support the treatment of adult-onset Pompe disease with alglucosidase alpha most recently in February 2011. The Committee considered evidence from a prospective observational cohort study specifically looking at the effect of alglucosidase alpha treatment on juvenile-onset Pompe disease (Van Capelle et al. Neuromuscul Disord 2010; 12:775-82). The Committee noted that the authors reported that five patients aged between 5 and 16 years treated with 20 mg/kg alglucosidase alpha every two weeks over a three year period showed no deterioration was seen in lung function and muscle strength and small gains were made by some patients.

- 3.48 The Committee considered a long term prospective observational, non-randomised cohort study involving 24 patients including 7 juveniles and 17 adults in which patients received bi-weekly infusions of alglucosidase alpha (20 mg/kg) for at least 36 months (Bembi et al. *J Inherit Metab Dis* 2010; 33:727-35). Members noted that the authors reported that compared to baseline, patients had significant improvements in motor function (as assessed by Walton scale) and 6 minute walk test at 3 years. The Committee noted that there was a great variation in results, especially for the adult population. Committee considered that in both juvenile and adult patients, gains were made in the first 12 months and then stabilised over the next 2 years (which is similar to the pattern observed in the pivotal Van der Ploeg et al. 2010 trial which PTAC reviewed in Feb 2011). The Committee noted that muscle strength improved only in juvenile patients and adult patients with mild to moderate disease severity while the 6 minute walk test response improved across all patients. The Committee noted that forced vital capacity and FEV1, remained stable and fewer patients required ventilator support and for less time compared with baseline. The Committee considered that there appeared to be a consistent effect on surrogate endpoints in all groups but the effect across patients was very variable.
- 3.49 The Committee considered a retrospective observational cohort study by Güngör et al. (*J Inherit Metab Dis* 2011; 3: 441 abstract and poster) which looked at the impact of alglucosidase alpha treatment on survival in 196 patients with adult-onset Pompe disease compared with an historic control group of 75 patients who had never received ERT. The Committee noted that the authors suggested that ERT extended lifespan with mortality reported to be 36% in the untreated group compared to 9% in the treated group. The Committee noted the data it was reviewing was abstract and poster only and so it could not review the quality of the study. The Committee noted that the median treatment duration was 4 years and median follow up time was 6 years. The Committee noted the authors concluded that a longer follow up was needed to elucidate the relationship between ERT, disease severity and survival of adults with Pompe disease.
- 3.50 The Committee considered that the evidence suggests that the optimum dose of alglucosidase alpha is 20mg/kg with no added benefit of higher doses. The Committee noted that PHARMAC have carried out a cost utility analysis for alglucosidase alpha in patients with adult-onset Pompe disease which indicated that it was cost-ineffective relative to other funding options.
- 3.51 The Committee considered that the claim by the supplier that alglucosidase alpha was 'life-saving' is misleading to patients and not supported by the evidence.
- 3.52 Overall, the Committee considered that the quality of the evidence for alglucosidase alpha in the treatment of infantile, juvenile and adult-onset Pompe disease was poor and the strength weak to moderate. The Committee considered that the evidence supports the benefit of treatment on some surrogate end points, however the long term effect on morbidity and mortality is still unknown. The Committee considered that there is little evidence to support treatment of patients with established disease and with irreversible end organ disease. The Committee noted the significant unmet health need faced by patients with Pompe disease, but considered this to be outweighed by the lack of evidence for clinically significant benefit and the disproportionately high cost of disease-modifying treatment.

4 Sorafenib for advanced hepatocellular carcinoma and second line metastatic renal cell carcinoma

Application

- 4.1 The Committee considered an application from Bayer New Zealand Ltd for the listing of sorafenib tosylate (Nexavar) on the Pharmaceutical Schedule for the treatment of patients with inoperable advanced hepatocellular carcinoma (HCC) with preserved liver function (Child Pugh score 5-7) and second line treatment of patients with advanced renal cell carcinoma (RCC) following treatment failure on, or intolerance to, sunitinib or other targeted treatments.

Recommendation

- 4.2 The Committee **recommended** that sorafenib should be listed on the Pharmaceutical Schedule as a first line treatment option in patients with advanced HCC who cannot benefit from resection, transplantation, ablation or transarterial chemoembolism and still have preserved liver function (Child Pugh A). Members gave this recommendation a low priority. The Committee further **recommended** that the application be referred to its Cancer Treatments Subcommittee for review and advice on appropriate Special Authority criteria.
- 4.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule,*
- 4.4 The Committee **recommended** that the application for second line funding of sorafenib for patients with advanced RCC be declined.
- 4.5 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 budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 4.6 The Committee noted that it had previously reviewed the funding of sorafenib for patients with advanced, inoperable, hepatocellular carcinoma (HCC) and first line treatment of patients with advanced renal cell carcinoma (RCC) and recommended both applications be declined.
- 4.7 The Committee noted that in this new application the supplier proposes that:

- sorafenib be funded for the treatment of patients with inoperable HCC with preserved liver function (Child Pugh score 5-7), and
- sorafenib be funded for the second line treatment of patients with metastatic RCC, following disease progression on, or intolerance to, at least 1-2 cycles of sunitinib.

4.8 [Withheld under s (9(2)(j)) of the OIA]

4.9 The two indications (HCC and RCC) were discussed separately.

Hepatocellular Carcinoma

- 4.10 The Committee considered that there was a high unmet clinical need for new effective treatments for patients with advanced HCC. Members noted that HCC usually occurs in people with a degree of liver cirrhosis most often associate with hepatitis B or C infection. Members noted that the incidence of HCC in Asian, Maori and Pacific Islanders was high consistent with the higher incidences of hepatitis B and C infection in these populations compared with NZ Europeans.
- 4.11 The Committee noted that in its resubmission the supplier reiterates evidence previously considered by PTAC (SHARP, Llovet et al NEJM 2008;359:378-90 and an Asia-pacific Study, Chen et al Lancet Oncology 2009;10:25-34) and provides new evidence from a number of other clinical trials. Members considered that the new evidence provided was weak and of poor quality, comprising mainly unpublished abstracts and slide presentations from small, single arm prospective or retrospective observational studies with the exception of one randomised controlled study comparing sorafenib with sunitinib, which was stopped early because of a higher incidence of serious adverse events in patients treated with sunitinib.
- 4.12 The Committee considered that evidence from the SHARP and Asia-Pacific studies demonstrated that sorafenib was associated with a small survival gain (2-3 months) compared with best supportive care. However, members noted that there was no difference in time to symptomatic progression and no evidence of improved quality of life for patients treated with sorafenib and response rates were very low. Members noted that sorafenib was associated with significant adverse effects including diarrhoea, hand foot syndrome, alopecia, rash, weight loss, anorexia, fatigue and thrombocytopenia.
- 4.13 The Committee considered that the new evidence supported the findings of the SHARP and Asia-Pacific studies and demonstrated that the degree of cirrhosis appeared to be an important predictor of outcome in patients treated with sorafenib for advanced HCC. Members noted that overall survival was longer in patients with patients with preserved liver function (Child Pugh A, score 5-6) as compared with patients with more severe liver disease (Child Pugh B (score 7-9) or higher).
- 4.14 The Committee considered that even with the revised commercial proposal sorafenib remained a very costly treatment that provided a relatively small gain in length of life for HCC patients. Members considered that the absence of quality of life data

prevented meaningful evaluation of sorafenib's true benefit or value to patients. This notwithstanding, members were prepared to offer limited support to the application in light of the evidence for a small increase in overall survival and the absence of any other disease-modifying treatment for this disease.

Renal Cell Carcinoma

- 4.15 The Committee noted that, in addition to reiterating first line RCC evidence previously considered (the TARGET study - Escudier et al NEJM 2007 ;356;2;125-134 and updated in Escudier et al J Clin Oncol 2009;27:3312-3318, and study 100391 - Ratain et al. J Clin Oncol 2006;24:2505-2512), the supplier had also provided new evidence for the use of sorafenib as a second line treatment of RCC following treatment failure, or intolerance to, sunitinib or other 'targeted' treatments. Members considered that the new evidence provided was weak and of poor quality, comprising mainly unpublished abstracts and small, prospective and retrospective single arm studies and expanded access programmes reporting outcomes from various sequencing strategies with sunitinib and sorafenib or other targeted treatments.
- 4.16 The Committee considered that collectively these studies reported progression free survival in the region of 3-4 months for patients treated with sorafenib as a second line treatment for RCC. However, members noted that because there were no randomised controlled studies it was not possible to determine if sorafenib provided any benefit compared with best supportive care in this setting. Members considered that sorafenib may extend progression free survival by a small amount but it could be associated with significant and sometime unpleasant adverse events and its effect on quality of life was unknown.
- 4.17 The Committee noted that, in general, it did not support the funding of expensive agents with little benefit, for second line treatment of patients. The Committee considered that it may be reasonable to offer sorafenib as a second line treatment option for patients intolerant of sunitinib whose disease had not progressed on sunitinib; however, members noted that there was little evidence to support this.

5 Everolimus for metastatic renal cell carcinoma

Application

- 5.1 The Committee considered an application from Novartis NZ Ltd for the listing of everolimus (Afinitor) on the Pharmaceutical Schedule for the treatment of patients with advanced Renal Cell Carcinoma (HCC) in patients who have received prior VEGF-targeted therapy (i.e. second line therapy).
- 5.2 The Committee also considered a separate submission from a clinician on behalf of the Genito-Urinary Special Interest Group of the NZ Association of Cancer Specialists (GU SIG). In its Submission GU-SIG requested funding of everolimus as a first line treatment for certain patients with advanced RCC in addition to second line funding in patients who have received prior (as per the suppliers submission).

Recommendation

- 5.3 The Committee **recommended** that the applications from the supplier and GU-SIG for second line funding of everolimus for patients with advanced RCC who have received prior VEGF-targeted therapy be declined.
- 5.4 The Committee further **recommended** that the application from GU-SIG for first line funding of everolimus for patients with advanced RCC be declined. The Committee noted that it would welcome a resubmission for first line funding of everolimus once data from the relevant clinical trial (RECORD-3) becomes available.
- 5.5 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

- 5.6 The Committee noted that everolimus is an orally administered mammalian target of rapamycin (mTOR) inhibitor indicated for the treatment of patients with advanced RCC who have received prior VEGF-targeted therapy. Members noted that everolimus had a different target to currently funded sunitinib treatment.
- 5.7 The Committee noted that key evidence supporting the use of everolimus as a second line treatment comprised a Phase III, randomised, double-blind study (RECORD-1 (Renal Cell cancer treatment with Oral RAD001 given Daily), Motzer et al. Lancet 2008;372:449–56 and Motzer et al. Cancer 2010;116:4256–65). Members noted that this study compared everolimus 10 mg/day with placebo, both in conjunction with best supportive care, in patients with metastatic RCC whose disease had progressed despite prior treatment with VEGF-inhibitors therapy (sunitinib, sorafenib, or both sunitinib and sorafenib). Members noted that prior therapy with bevacizumab, cytokines and chemotherapy were also permitted.
- 5.8 The Committee noted that 416 patients were randomised 2:1 to receive everolimus (n=277) or placebo (n=139) with treatment in both groups continued on treatment until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Members noted that following documented disease progression, on the basis of investigator assessment, patients were unblinded and those initially randomised to placebo were permitted to crossover to receive open-label everolimus. Members further noted that following a second pre-planned interim analysis which demonstrated a significant difference in the primary endpoint (progression free survival (PFS) documented with RECIST and assessed via a blinded, independent central review) between the treatment groups (101 [37%] events in the everolimus group, 90 [65%] in the placebo group; hazard ratio 0.30, 95% CI 0.22–0.40, p<0.0001; median progression-free survival 4.0 [95% CI 3.7–5.5] vs 1.9 [1.8–1.9] months) the study was unblinded and the remaining 6 patients still on placebo were permitted to cross-over to

open label everolimus. Members noted that in total 80% of patients initially randomised to placebo crossed over to everolimus.

- 5.9 The Committee noted that in the final analysis median PFS was 3 months longer in patients treated with everolimus compared with placebo (4.9 months everolimus vs 1.9 months placebo HR, 0.33; 95% CI, 0.25-0.43; P <0.001). However, there was no meaningful difference in quality of life between the patient groups and there was no difference in median overall survival. Members considered that, given the large number of placebo patients who received open-label everolimus, overall survival results were confounded.
- 5.10 The Committee noted that in an attempt to correct, or account for, this significant cross-over the supplier had undertaken an analysis of overall survival using a rank-preserved structural failure time method (RPSFT). Members considered that such analysis was inevitably subject to bias and should only be considered exploratory due to its post-hoc implementation. In general, members considered that in the absence of a published independent analysis of the raw data using the RPSFT if was not possible to determine if the supplier had implemented the methodology correctly. Overall, members considered the RPSFT analysis of overall survival to be of low strength and quality.
- 5.11 The Committee considered that given the high percentage of cross-over and the post hoc exploratory nature of the RPSFT analysis it was not possible to draw a firm conclusion concerning the effect of everolimus on overall survival time in the RECORD-1 study.
- 5.12 The Committee noted that in general everolimus was quite well tolerated, with grade 3/4 events relatively infrequent (5-6%). Members noted that 8% of patients experienced pneumonitis, a known mTOR class effect, and everolimus was also associated with a higher incidence stomatitis, anaemia, asthenia, fatigue, cough, diarrhoea and rash.
- 5.13 The Committee could not identify a subgroup of patients who may experience long term disease control with everolimus noting that in RECORD-1 virtually all patients who received everolimus had progressed by 14 months and there was no evidence of a long 'tail' on the Kaplan-Meier curve that would be suggestive of the presence of a patient subgroup that would likely do better.
- 5.14 The Committee noted that the supplier's own economic analyses implied that everolimus was likely to have poor cost-effectiveness relative to other funding options.
- 5.15 The Committee considered that, although there was a high unmet need for effective second line treatment options in patients with advanced RCC following disease progression of sunitinib, in general, it did not support the funding of expensive agents with marginal benefit, in this setting.
- 5.16 The Committee considered although evidence provided by the GU-SIG demonstrated a benefit for temsirolimus, another mTOR inhibitor, in the first line treatment of patients with advanced RCC, there was no evidence to support the use of everolimus in this setting at present. The Committee noted that it would welcome an application for the funding of temsirolimus as a first line treatment option and that a phase III first-line

study of everolimus was ongoing (RECORD-3) and it would welcome a re-submission once this data is mature.

6 Sunitinib for Imatinib Refractory Gastro Intestinal Stromal Tumours

Applicaton

- 6.1 The Committee considered an application from Pfizer to widen funded access to sunitinib (Sutent) listed in the Pharmaceutical Schedule to include treatment of patients with gastrointestinal stromal tumour (GIST) that is refractory to imatinib due to treatment failure or intolerance.

Recommendation

- 6.2 The Committee **recommended** that the listing of sunitinib on the Pharmaceutical Schedule should be widened to include funding for patients with GIST after failure of imatinib treatment, due to resistance or intolerance. Members gave this recommendation a low priority. The Committee further **recommended** that the application be referred to its Cancer Treatments Subcommittee for review and advice on appropriate Special Authority criteria.
- 6.3 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

- 6.4 The Committee considered that currently many patients with GIST who show disease progression on funded imatinib 400 mg daily would receive additional 'top up' imatinib, to 800 mg daily, free of charge from its supplier (Novartis).
- 6.5 The Committee noted that it had previously reviewed the funding of sunitinib for imatinib refractory GIST and had recommended the application be declined. Members noted that in its resubmission the supplier provides further follow-up data in the form of a slide presentation by Schoffski et al. from the European Society of Medical Oncology (ESMO) 2008 meeting, and a clinical study report, of the final analysis of the pivotal Phase III study A6181004. Members noted that this study was a randomised, double blind, placebo controlled clinical trail with patients randomised 2:1 to receive sunitinib 50 mg once daily or placebo until disease progression. Members noted that at disease progression patients were unblinded and permitted to cross over to open label sunitinib. Members further noted that following the interim analysis (published by Demitri et al Lancet 2006;368:1329) the study was unblinded at the recommendation of the Independent Data and Safety Monitoring Board and all remaining patients still on placebo were permitted to cross-over to open label sunitinib. The Committee

considered that the A6181004 enrolled a healthier population than would be expected in clinical practice.

- 6.6 The Committee noted that at the interim analysis median time to tumour progression was significantly longer in patients treated with sunitinib compared with placebo (27.3 weeks compared with 6.4 weeks HR 0.33, 95% CI 0.23-0.47, $p < 0.0001$) and other secondary endpoints were also improved with sunitinib. Members noted that at the time of interim analysis median overall survival data was not available due to immaturity of the data, however, mean survival at the time favoured sunitinib (HR 0.49 95% CI 0.29-0.83, $p = 0.007$).
- 6.7 The Committee noted that due to the considerable cross-over in the study, with 83% of all placebo patients crossing over to sunitinib at some point, interpretation of longer term overall survival data was severely confounded and subject to selection bias. Members noted that in an attempt to correct, or account for, this significant cross-over the supplier had undertaken an analysis of overall survival using a rank-preserved structural failure time method (RPSFT). Members considered that such analysis was inevitably subject to bias and should only be considered exploratory due to its post-hoc implementation. In general, members considered that in the absence of a published independent analysis of the raw data using the RPSFT if was not possible to determine if the supplier had implemented the methodology correctly. Overall, members considered the RPSFT analysis of overall survival to be of low strength and quality.
- 6.8 The Committee considered that given the high percentage of cross-over and the post hoc exploratory nature of the RPSFT analysis it was impossible to draw any meaningful conclusions concerning the effect of sunitinib on overall survival time in the A6181004 study.
- 6.9 The Committee considered that GIST was a well characterised disease and the use of targeted treatments such as imatinib and sunitinib had good molecular rationale. Members noted that in this setting because lesions are cystic maintaining stable disease was an important treatment goal and would likely lead to improved quality of life.

7 Gefitinib for first line treatment of non-small cell lung cancer

Application

- 7.1 The Committee considered an application from AstraZeneca for the listing of gefitinib (Iressa) for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer expressing epidermal growth factor receptor tyrosine kinase (EGFR) activating mutations.
- 7.2 The Committee also considered a separate submission from a clinician requesting funding of EGFR tyrosine kinase inhibitors (erlotinib (Tarceva, Roche Products NZ Limited) and/or gefitinib) for first-line use in advanced adenocarcinoma of the lung with activating mutations of the EGFR. In addition, the Committee considered information provided by the National Health Committee regarding EGFR testing.

Recommendation

- 7.3 The Committee **recommended** that gefitinib should be listed on the Pharmaceutical Schedule for the first line treatment of patients with locally advanced or metastatic NSCLC expressing EGFR activating mutations. Members gave this recommendation a medium priority.
- 7.4 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*
- 7.5 The Committee further **recommended** that the Special Authority criteria for second line funding of erlotinib be amended to limit funding to patients with locally advanced or metastatic NSCLC expressing EGFR activating mutations. Members gave this recommendation a high priority.
- 7.6 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

Discussion

- 7.7 The Committee noted that lung cancer is the leading cause of cancer death in New Zealand causing 19% of all cancer deaths and one third of all Maori cancer deaths. Members noted that NSCLC is the most common type of lung cancer and the majority (up to 70%) of patients present with advanced stage IIIB or IV disease at diagnosis where survival rates are very poor.
- 7.8 The Committee noted that it, and its Cancer Treatments Subcommittee (CaTSoP), had previously considered the funding of gefitinib for third and second line treatment of advanced NSCLC and recommended it be declined. However, members noted that at that time the applications and evidence were not limited to disease expressing EGFR activating mutations. The Committee noted that in 2004 CaTSoP considered that a hypothesis implicating EGFR mutations as important predictors of response needed to be tested prospectively.
- 7.9 The Committee noted that understanding of the molecular pathways of NSCLC has advanced rapidly over the last few years and considered that a recent review article covered the topic well (Ellis et al. J Thor Onc 2011;6:1379-1391). Members considered that current research indicated that specific activating mutations in the tyrosine kinase domain of EGFR (exon 19 deletions and L865R point mutations in exon 21) were associated with increased responsiveness to EGFR inhibitors gefitinib and erlotinib.
- 7.10 The Committee noted that these activating mutations were present in a relatively small proportion of all NSCLC patients but were more common in adenocarcinomas compared with squamous cell carcinomas. Members considered that approximately 50% of NSCLCs were adenocarcinomas, of which 10-17% could be expected to

express EGFR activating mutations, compared with <4% of squamous cell carcinomas. Members further noted that the smoking-related adenocarcinomas were less likely to express EGFR activating mutations compared with non-smoking-related adenocarcinomas. Overall, members considered that approximately 5% of all advanced stage IIIB or IV NSCLC would express EGFR activating mutations.

- 7.11 The Committee reviewed evidence from 4 randomised controlled studies for gefitinib and two studies for erlotinib. Overall members considered that the results across these six studies were very consistent and the evidence demonstrated that compared with standard platinum based chemotherapy tyrosine kinase inhibitor treatment improved progression free survival by around 3-5 months in patients with stage IIIB or IV NSCLC expressing EGFR activating mutations. Importantly, members noted that in one study (IPASS Fukuoka et al J Clin Oncol 2011;29:2866-74) patients without EGFR activating mutations did worse with the tyrosine kinase inhibitor treatment (in this case gefitinib) compared with platinum based chemotherapy.
- 7.12 The Committee noted that, where undertaken, quality of life assessments were improved with tyrosine kinase inhibitor treatment in patients with EGFR activating mutations, however, there was no evidence supporting improved overall survival. However, members considered that this was likely due to extensive cross over in the studies.
- 7.13 The Committee noted that despite good initial responses many patients would develop resistance to EGFR inhibitors. Members noted that there was no evidence to support the use of a second tyrosine kinase inhibitor after failure of a prior tyrosine kinase inhibitor (erlotinib after gefitinib or vice versa). The Committee considered that the efficacy and safety of gefitinib and erlotinib were the same or similar.
- 7.14 The Committee noted that the current funding of erlotinib for second line treatment of patients with NSCLC was implemented prior to the clear understanding for the role of EGFR activating mutations in determining treatment response. Members noted that currently most oncologists were using an expensive 'trial of therapy' approach with erlotinib rather than undertaking EGFR activating mutation testing prior to commencing treatment. Members considered that treating EGFR activating mutation negative patients with erlotinib was not appropriate and that these patients may have a better response to standard chemotherapy.
- 7.15 The Committee considered that all patients with NSCLC should undergo EGFR activating mutation testing in order to determine appropriate treatment. Members noted, and supported, the National Health Committee's review of national funding of EGFR activating mutation testing. Members noted the American Society of Clinical Oncology has recently published a provisional clinical option of EGFR mutation testing (Keedy et al. J Clin Oncol 2011;29:2121-27 in which it does not recommend immunohistochemistry (IHC) and fluorescent in situ hybridisation (FISH) methods. Members agreed with these recommendations and considered that because the presence of specific mutations, rather than copy number, were predictive of response EGFR activating mutation testing should be done using PCR methodology.
- 7.16 The Committee considered that, if funded, gefitinib would replace platinum based doublet chemotherapy as standard first line treatment in patients with locally advanced/metastatic NSCLC expressing EGFR activating mutations. Members

considered that such patients would then be treated with platinum based doublet chemotherapy, single agent chemotherapy or best supportive care on disease progression. Members considered that in this patient group first line treatment with gefitinib would essentially replace second line treatment with erlotinib. Members considered that the costs of funding EGFR activating mutation testing all NSCLC patients should be included in any budget impact and cost-utility analyses of its funding recommendations.

8 Ticagrelor for acute coronary syndrome

Application

- 8.1 The Committee reviewed an application from AstraZeneca for the listing of ticagrelor (Brilinta) on the Pharmaceutical Schedule for the treatment of acute coronary syndrome (unstable angina, ST-elevation myocardial infarction (STEMI), or non-ST-elevation myocardial infarction (NSTEMI)) in patients who are medically managed, managed with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

Recommendation

- 8.2 The Committee recommended that the application for ticagrelor be referred to the Cardiovascular Subcommittee for consideration, including for further advice on the extent that the outcomes of the PLATO and TRITON-TIMI 38 trials (for prasugrel hydrochloride) would be achieved in clinical practice; and the identification of the patient groups that would receive the greatest clinical benefit from ticagrelor and the length of therapy that would result in the greatest clinical benefit being obtained.

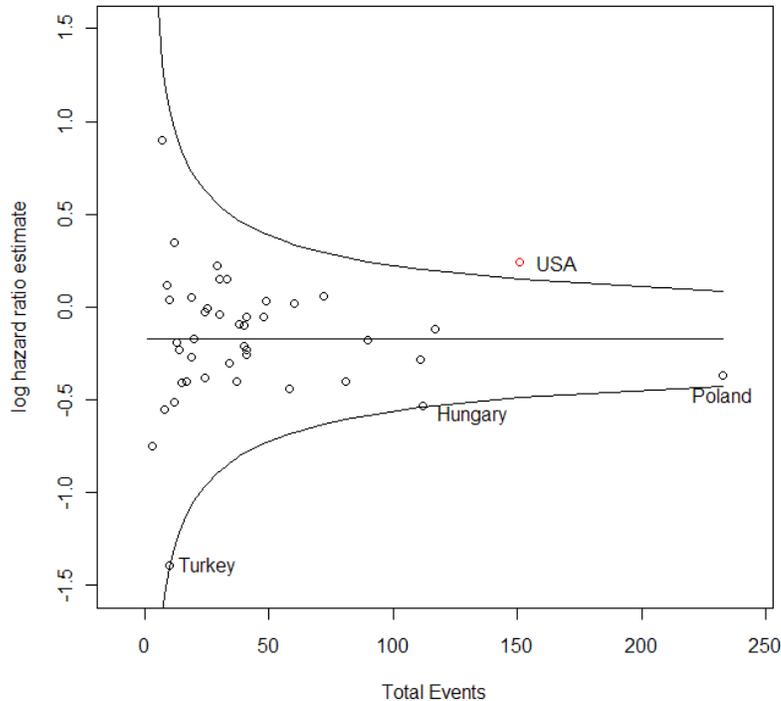
Discussion

- 8.3 The Committee noted that currently clopidogrel is funded without Special Authority restriction and can be used in combination with aspirin for patients with acute coronary syndromes (ACS).
- 8.4 The Committee noted a number of relevant trials including DISPERSE (Husted et al. Eur Heart J 2006; 27: 1038-47), DISPERSE2 (Cannon C et al. J Am Coll Cardiol 2007;50: 1844-51), PLATO (Wallentin L et al. N Engl J Med 2009;361:1045-57), publications from large number of sub-group analyses, ONSET/OFFSET study (Gurbel et al. Circulation 2010; 121: 1169-1171) and RESPOND study (Gurbel et al. Circulation 2010; 121: 1188-1199) which was not provided with the submission.
- 8.5 The Committee noted that the DISPERSE2 (Cannon C et al. J Am Coll Cardiol 2007;50: 1844-51) trial which compared 90 mg and 180 mg twice daily doses of ticagrelor to a once daily 75 mg dose of clopidogrel found that at 4 weeks, there was no significant difference in efficacy or bleeding side-effects between the three treatment arms, although there was a statistically insignificant trend to reduced myocardial infarctions (MI) with ticagrelor. Higher frequency of ventricular pauses was noted with both ticagrelor groups but this was only statistically significant with 180 mg group. In addition the Committee noted that there was an increased incidence of dyspnoea and other drug related side effects with ticagrelor.

- 8.6 The Committee noted the PLATO trial (Wallentin L et al. N Engl J Med 2009;361:1045-57) was a multicentre, double-blind, double dummy randomised trial involving 18,624 patients admitted to hospital with an acute coronary syndrome, with or without ST-segment elevation. The Committee noted that patients were randomised to two treatment arms and received either ticagrelor 90 mg twice daily or clopidogrel 75mg once daily over a period of 12 months in addition to other therapies including aspirin. The Committee noted that for the primary endpoint of composite death from vascular causes, myocardial infarction or stroke, patients who received ticagrelor had significantly lower event rates than those who received clopidogrel, 9.8% versus 11.7% (1.9% ARR, NNT 53, HR 0.84, 95% CI 0.77-0.92, p<0.001). In addition there was a reduction in incidence of stent thrombosis favouring ticagrelor. The Committee noted that there was no significant difference in the rates of major bleeding between the two treatment arms; ticagrelor arm 11.6% and clopidogrel arm 11.2% (p=0.43). The Committee however noted that ticagrelor was associated with a higher rate of major bleeding unrelated to coronary artery bypass grafting (4.5% versus 3.8%, p=0.03), including higher rates of fatal intracranial bleeding (0.1% versus 0.01%, p=0.02).
- 8.7 The Committee noted that in the PLATO trial the primary clinical endpoint curves for ticagrelor and clopidogrel started to appear after 30 days and were continuing to separate up to 12 months and that the sponsor considered that this supported ticagrelor use up to and beyond 12 months. The Committee noted that divergence up to 12 months was not consistent with the trial results for clopidogrel (Yusuf et al. N Engl J Med. 2001;345:494-502) or prasugrel hydrochloride (Wiviott SD, et al. N Engl J Med. 2007;357:2001-15) and considered that there was no obvious explanation for this difference. The Committee also noted the lack of consensus in optimal duration of dual antiplatelet therapy after PCI and recent PRODIGY trial results which were presented at the European Society of Cardiology 2011 congress which suggested that 6 months' treatment of clopidogrel may be more appropriate than 2 years treatment.
- 8.8 The Committee also noted that in predefined subgroup analysis there was no significant benefit in ticagrelor in patients who were on prior clopidogrel aspirin combination, when GpIIb/IIIa inhibitors were used, in non-Caucasians and in unstable angina. However the benefit of ticagrelor appeared to be attenuated in patients weighing less than the median weight for their sex (p=0.04 for interaction), patients not taking lipid lowering drugs (p=0.04 for the interaction) and North American patients (p=0.045 for the interaction).
- 8.9 The Committee considered that the results of the PLATO trial may be compromised by a number of limitations in the trial design which could result in a reduction in benefit compared with clopidogrel. These limitations included:
- 8.9.1 An inconsistent loading dose of clopidogrel. Only 19.6% of the patients in the clopidogrel arm and 13.7% in the ticagrelor arm received 600 mg of clopidogrel. 59.5% of the patients in the clopidogrel arm only received a 300-375mg loading dose.
- 8.9.2 Almost one third of patients receiving ticagrelor also received clopidogrel during the randomised treatment period.

- 8.9.3 The elimination of clopidogrel's compliance advantage due to it having once daily dosing when ticagrelor requires twice daily dosing – the clopidogrel arm was required to have twice daily dosing to ensure blinding.
- 8.9.4 Patients being allowed to stop the study protocol at their 6 or 9 month follow-up visit once the targeted number of primary endpoints had occurred even though the trial was intended to be for 12 months. PTAC noted that as a result patients received different treatment durations with the mean duration being 276¹ days (interquartile range of 179 to 365 days) rather than the reported 12 months and considered that the reported trial duration should have been 6 months with a small subgroup of patients continuing to 12 months. The Committee noted that according to FDA, 15% of patients had incomplete follow-up with regard to nonfatal cardiovascular events; specifically, these patients did not have a final clinic visit.
- 8.10 In relation to the results of the PLATO trials predefined subgroup analyses (see paragraph 13.8 above), the Committee noted the high number of both such prespecified analyses and post hoc analyses, and considered that results of all of the subgroup analyses need to be interpreted with some caution. The Committee considered that having multiple prespecified and post hoc subgroup analyses could increase the risk of play of chance.
- 8.11 The Committee noted a viewpoint article regarding paradoxical excess mortality in the PLATO trial which does not match with historical incidence rates and with no obvious explanation (Serebruany. Thrombosis and Haemostasis 2011; 105:752-759).
- 8.12 The Committee also reviewed the funnel plot of log hazard ratio by events per country generated by the FDA statistical review (Fiorentino. Clinical Efficacy Review, NDA 022433 Brilinta, ticagrelor. FDA, June 2010. Clinical efficacy review, page 95. Figure 24. Funnel plot by Country. Available at <http://www.fda.gov/downloads/Advisorycommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220192.pdf>).

¹ At its February 2012 meeting the Committee reviewed these minutes and made the following amendment. Paragraph 13.9.4 (8.9.4 in web version) change: “mean duration being 277 days” to “mean duration being 276 days”. Please refer to the February 2012 minutes at www.pharmac.govt.nz/PTAC/PTACminutes.



(reproduced from Fiorentino, p.95)

The Committee noted that Poland and Hungary were major outliers, and given their numbers of events they would have a large bearing on the overall results of the trial. Although these two countries accounted for only 21% of the patients, they were responsible for 46% of the endpoint events favouring ticagrelor. The Committee also considered that the management of ACS in New Zealand may well be different from the management in Poland and Hungary, thus making it difficult to interpret the overall findings from PLATO.

- 8.13 The Committee also noted that in the United States clopidogrel was superior to ticagrelor and that an explanation proposed for the lack of effect of ticagrelor in the United States was that a higher aspirin dose was used there. The Committee considered that if the higher dose of aspirin did indeed explain the outcome in the United States then a higher dose of aspirin in combination with clopidogrel might be considered as an alternative to ticagrelor, even though the higher dose of aspirin is not commonly used in New Zealand.
- 8.14 The Committee noted that there are no direct comparisons between ticagrelor and prasugrel hydrochloride but that an indirect meta analysis of prasugrel versus ticagrelor, while having some significant limitations, concluded that there was no difference in overall death, MI, stroke or their composite (Biondi-Zoccai et al. *Int J Cardiol* 2011;150:325-31). When the two treatments were compared, prasugrel was associated with significantly reduced risk of stent thrombosis ($p=0.02$) but ticagrelor was associated with reduced risk of major bleeding ($p=0.007$) and CABG-associated bleeding ($p=0.002$). However the Committee reiterated the limitations of an indirect meta analysis.
- 8.15 The Committee considered that although ticagrelor reversibly interacts with the platelet P2Y₁₂ ADP-receptor, there is currently no known antidote and in actual clinical practice

its reversible interaction provided little if any clinical benefit over clopidogrel. The Committee noted that according to its Medsafe datasheet, patients taking ticagrelor experienced more bleeding than those on clopidogrel when therapy was stopped within 1 day prior to surgery but those on ticagrelor had a similar rate of major bleeds compared to clopidogrel after stopping therapy two or more days before surgery.

- 8.16 The Committee considered that there were more adverse effects associated with ticagrelor. Dyspnoea occurred in 13.8% of ticagrelor patients compared with 7.8% patients on clopidogrel (number-needed-to-harm (NNH) 17) and this resulted in discontinuation of ticagrelor in 0.9% (for every 125 patients 1 discontinued). Ventricular pauses of more than 0.3 seconds occurred in 5.8% of ticagrelor patients compared with 3.6% of clopidogrel patients (NNH 46) at the end of 1 week but not at 30 days. There was no significant difference in syncope or pacemaker insertions between two groups. The Committee noted that PLATO excluded patients at risk of significant bradyarrhythmias and the likelihood of these side effects would be higher in routine clinical practice. The Committee also noted that patients who had fibrinolytic therapy within last 24 hours were also excluded.
- 8.17 The Committee noted that creatinine and uric acid levels were increased in patients on ticagrelor when compared with clopidogrel ($p < 0.001$) and returned to normal 1 month after discontinuation of study drug. Discontinuation of study drug due to adverse effects occurred more frequently with ticagrelor, 7.4% versus 6.0% with clopidogrel.
- 8.18 The Committee considered the potential disadvantages of ticagrelor that included twice daily administration, side effects including bradycardia, dyspnoea, general increase in bleeds including intracranial bleeding, raised uric acid, creatinine and potential for multiple drug interactions including CYP 3A4 and substrates (ketoconazole, clarithromycin, nefazodone, ritonavir, atazanavir, diltiazem, verapamil, simvastatin, atorvastatin) and inhibitors of p-glycoprotein (digoxin, cyclosporine).
- 8.19 The Committee considered that there may be potential benefit of ticagrelor over clopidogrel in Maori and Pacific people due to the genetic polymorphisms reducing the response to clopidogrel, but the clinical significance and potential benefit of other agents in this situation were unclear at this time.
- 8.20 Overall, the Committee considered that the benefit compared with harm provided by ticagrelor was small (absolute risk reduction of 1.9% (HR 0.84, 95% CI 0.77 to 0.92, $p < 0.001$)), probably no benefit in patients presenting with unstable angina and that there is some uncertainty as to whether the benefit portrayed in the PLATO study would eventuate in patients in clinical practice. The Committee also considered that ACS is not an area of urgent unmet clinical need as there are funded alternatives available. The Committee considered that ticagrelor is significantly more expensive than clopidogrel and the fiscal effect of listing ticagrelor would be high due to its higher price, the fact that it would be used instead of clopidogrel and the large potential patient population.
- 8.21 The Committee considered that the place in therapy of ticagrelor should be further considered by the Cardiovascular Subcommittee of PTAC. The Committee considered that this should include: (i) an indication from the Cardiovascular Subcommittee as to the quality of the evidence and its confidence as to whether the absolute risk reduction achieved in the PLATO trial would be achieved in clinical practice, (ii) whether the

Subcommittee would have greater confidence in the outcomes of the PLATO trial or the TRITON-TIMI 38 trial (Montalescot et al. Lancet 2009; 373(9665): 723-731) with prasugrel being achieved in clinical practice, and (iii) the identification of patient groups and lengths of treatment which would result in the greatest clinical benefit being obtained with ticagrelor for the purposes of targeting therapy to those with the highest clinical need and for periods where it would provide the greatest health benefit.

- 8.22 The Committee noted that the sponsor did provide full study report of DISPERSE 2 study but not the full PLATO study report in the submission. The full study report would have enabled the Committee to come to better conclusions on ticagrelor and considered that this should have been provided by the sponsor.

9 Prasugrel for STEMI patients primary PCI

Application

- 9.1 The Committee reviewed a PHARMAC staff memorandum regarding the listing of prasugrel hydrochloride on the Pharmaceutical Schedule for the treatment of ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention.

Recommendation

- 9.2 The Committee **recommended** that the application for prasugrel hydrochloride (Effient) for the treatment of ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention be declined.
- 9.3 The Decision Criteria particularly relevant to this recommendation are: *(iv) The clinical benefits and risks of pharmaceuticals.*

Discussion

- 9.4 The Committee noted that it had previously reviewed prasugrel on a number of occasions and that it had recommended that prasugrel be funded with low priority for patients who are undergoing percutaneous intervention (PCI) but are allergic to clopidogrel and for patients who experience stent thrombosis whilst on clopidogrel therapy. The Committee also noted that at its August 2011 meeting, it had requested that its recommendations for prasugrel in the subgroup of patients with ST-elevation myocardial infarction (STEMI) undergoing primary PCI be re-reviewed at this November 2011 meeting.
- 9.5 The Committee noted a number of relevant previous minutes including minutes from its February 2010, August 2010, February 2011 and August 2011 meetings and the minutes from the Cardiovascular Subcommittee meetings of October 2010 and September 2011 (draft minutes).
- 9.6 The Committee has previously noted that in the TRITON-TIMI trial (Montalescot G, et al. Lancet 2009;373: 723-731) in STEMI patients undergoing PCI the overall difference in primary endpoint (death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke) was 6.5% vs 9.5% at 30 days (HR 0.68 0.54-0.87 p=0.0017) and 10% vs 12.4% at 15 months (HR 0.79 0.65-0.97 p= 0.0221).

- 9.7 The Committee noted that the subgroup analysis of STEMI patients undergoing primary PCI in the TRITON-TIMI trial (Montalescot G, et al. Lancet 2009;373: 723-731) showed no statistically significant difference in the occurrence of the primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) when patients with primary PCI (those enrolled within 12 hours of onset of symptoms) were treated with clopidogrel or prasugrel at 30 days (8.2% versus 6.6%, HR 0.80, 95% CI 0.60-1.08, p=0.1440) or at 15 months (11.6% versus 10.2%, HR 0.87, 95% CI 0.68-1.11, p=0.2662).
- 9.8 The Committee also noted that the occurrence of the primary endpoint was significantly less in the prasugrel arm in the secondary PCI cohort at 30 days (12.3% versus 6.4%, HR 0.50, 95% CI 0.34-0.76, p=0.0008) and after 15 months (14.1% versus 9.6%, HR 0.65, 95% CI 0.46-0.92, p=0.0154). The Committee however considered that when testing for heterogeneity was performed on the 15-month results for the primary and secondary PCI cohorts, the effect was not statistically significant. The Committee considered that this finding casts doubt on the actual differentiation of results for the primary and secondary PCI cohorts in the occurrence of the primary endpoint.
- 9.9 The Committee considered that there is currently limited evidence for use of prasugrel in the subgroup of STEMI patients undergoing primary PCI. The Committee considered that although a significant improvement was seen in the one third of STEMIs treated with delayed PCIs, this group also had a delayed clopidogrel administration, which would not be considered to be current standard of care. The Committee considered that there would be time to adequately load clopidogrel in STEMI patients undergoing secondary PCI.

10 Tiotropium amendment to SA criteria

Application

- 10.1 The Committee reviewed a request from Boehringer Ingelheim for a number of changes to be made to the Special Authority criteria applying to tiotropium.

Recommendation

- 10.2 The Committee **recommended** that the applicant for Special Authority be changed from “a general practitioner or relevant specialist” to “any relevant practitioner” and that the format for recording lung function tests be consistent between the initial application or a renewal, with a medium priority.
- 10.3 The Committee **recommended** that the requests to change the breathlessness scale from Grade 4 or Grade 5 to \geq Grade 3; to change the specific reference to “a dose of 40 mcg ipratropium q.i.d. for one month” as a prerequisite and replacing it with “has trialled a short acting bronchodilator” and to remove the requirement to state lung function at the time of renewal be declined.
- 10.4 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;*

Discussion

- 10.5 The Committee noted that, at their February 2011 meeting they had declined an application from Boehringer Ingelheim to widen access to tiotropium.
- 10.6 The Committee noted that the only new paper to be included in this application was a full copy of the Vogelmeier et al paper, Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD (N Engl J Med. 2011;364:1093-1103). Preliminary results from this paper had been reviewed at the February meeting.
- 10.7 The Committee noted Vogelmeier et al had compared one years treatment with either tiotropium or salmeterol in patients with moderate to severe COPD (ie patients with an FEV₁ of <70% and an FEV₁/FVC of <70%). In this study 48% of the tiotropium patients were GOLD 2; 43% were GOLD 3 and 9% were GOLD 4. 50% of the salmeterol patients were GOLD 2, 42% were GOLD 3 and 8% GOLD 4. The trial indicated that, in patients with moderate to very severe COPD, tiotropium was superior in increasing the time to the first severe exacerbation.
- 10.8 The Committee noted that the Vogelmeier trial indicated tiotropium to be most effective in those patients with severe disease and those with a low BMI. Mortality was 1.7% in the tiotropium group and 2.1% in the salmeterol group. The Committee noted that while the Vogelmeier trial is a well designed trial it does not address the changes to the Special authority criteria.
- 10.9 Members considered that it would be appropriate for nurse prescribers specialised in the management of COPD to prescribe tiotropium. The Committee considered that there would be no difference in the level of prescribing if nurse practitioners were able to prescribe tiotropium. By changing the applicant name from General Practitioner to Relevant Practitioner, nurse prescribers will be able to apply for Special Authorities for tiotropium.
- 10.10 The Committee considered that there was no evidence provided that showed an added benefit for a change in the Special Authority criteria from Grade 4 or 5 breathlessness to Grade 3 or greater. The Committee considered that a change in the breathlessness scale would lead to an increase in patient numbers and recommended that this criterion remain unchanged.
- 10.11 The Committee considered removing the specific reference to ipratropium in the Special Authority criteria and replacing it with reference to short acting bronchodilators, as requested by Boehringer Ingelheim's application. The Committee discussed that ipratropium had specifically been included in the Special Authority as requiring an initial response to an anticholinergic agent as opposed to a beta-2 agonist benefits and recommended that there be no change to this criterion.
- 10.12 The Committee considered that the way in which the lung function is recorded on the current form is confusing as the formats for reporting FEV₁ at the time of the initial application and renewal differ, and recommended that they be changed so that they are recorded in the same manner. The format suggested within Boehringer Ingelheim's application seemed less confusing than the current special authority FEV1 format.

11 Adalimumab for fistulising Crohns disease, including access criteria for psoriasis and Crohns disease

Part I: Adalimumab for fistulising Crohn's disease

Application

- 11.1 The Committee reviewed an application from Abbott Laboratories New Zealand for the funding of adalimumab (Humira) on the Pharmaceutical Schedule for the treatment of fistulising Crohn's disease.

Recommendation

- 11.2 The Committee **recommended** that the Special Authority criteria for adalimumab for the treatment of Crohn's disease be amended to include fistulising disease with a medium priority as follows (additions in bold, deletions in strikethrough):

Initial application — (Crohn's disease) only from a gastroenterologist. Approvals valid for 3 months for applications meeting the following criteria:

- 1 All of the following:
 - 1.1 Patient has severe active Crohn's disease; and
 - 1.2 Any of the following:
 - 1.2.1 Patient has a Crohn's Disease Activity Index (CDAI) score of greater than or equal to 300; or
 - 1.2.2 Patient has extensive small intestine disease affecting more than 50 cm of the small intestine; or
 - 1.2.3 Patient has evidence of short gut syndrome or would be at risk of short gut syndrome with further bowel resection; or
 - 1.2.4 Patient has an ileostomy or colostomy, and has intestinal inflammation; and
 - 1.3 Patient has tried but had an inadequate response to, or has experienced intolerable side effects from, prior systemic therapy with immunomodulators at maximum tolerated doses (unless contraindicated) and corticosteroids; and
 - 1.4 Surgery (or further surgery) is considered to be clinically inappropriate;

Initial application – (fistulising Crohn's disease) only from a gastroenterologist.

Approvals valid for 6 months for applications meeting the following criteria:

Patient has confirmed Crohn's disease; and

1. **Either**
 - 1.1. **Patient has one or more complex externally draining enterocutaneous fistula(e); or**
 - 1.2. **Patient has one or more rectovaginal fistula(e); and**
2. **An adequate trial of conventional treatment has not been successful (defined as at least 4 months therapy with an adequate dose of thiopurine or methotrexate);**
3. **Patient must be reassessed for response to treatment after 4 months of therapy. Only 4 months of treatment will be funded under initial approval.**

A Recent Baseline Fistula Assessment should be completed

Renewal — (Crohn's disease) only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

- 1 Either:
 - 1.1 Applicant is a gastroenterologist; or
 - 1.2 Applicant is a Practitioner and confirms that a gastroenterologist has provided a letter, email or fax recommending that the patient continues with adalimumab treatment; and
- 2 Either:
 - 2.1 Either:
 - 2.1.1 CDAI score has reduced by 100 points from the CDAI score when the patient was initiated on adalimumab; or
 - 2.1.2 CDAI score is 150 or less; or
 - 2.2 Both:
 - 2.2.1 The patient has demonstrated an adequate response to treatment but CDAI score cannot be assessed; and
 - 2.2.2 Applicant to indicate the reason that CDAI score cannot be assessed; and
- 3 Adalimumab to be administered at doses no greater than 40 mg every 14 days.

Renewal – (fistulising Crohn’s disease) only from a gastroenterologist or medical practitioner on the recommendation of a gastroenterologist. Approvals valid for 6 months meeting the following criteria:

Either:

1. **the number of open draining fistulae have decreased from baseline by at least 50%; or**
2. **there has been a marked reduction in drainage of all fistula(e) from baseline as demonstrated by a reduction in the Fistula Assessment score, together with less induration and patient reported pain.**

- 11.3 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

- 11.4 The Committee noted that adalimumab is currently listed in the Pharmaceutical Schedule for patients with Crohn’s disease who have a Crohn’s Disease Activity Index (CDAI) score of > 300. The Committee considered that a proportion of patients with localised severe fistulising disease and no or limited luminal disease do not currently meet the funding criteria to use adalimumab on the basis of CDAI score. The Committee noted that a number of these patients would receive infliximab however access across DHB hospitals varies.
- 11.5 The Committee considered that the main relevant evidence supplied in the application is a study of adalimumab in the subpopulation of the CHARM study (Colombel et al. *Gastroenterology* 2007;132:52-65) who had fistulising disease. This group of 117 patients were randomised into three arms (placebo, 40 mg adalimumab once weekly

or 40 mg adalimumab every other week). The randomisation was not stratified for the presence of fistulising disease, resulting in the number in each group being placebo n=47, 40 mg weekly n=40 and 40 mg every other week n=30. A CDAI of greater than 220 was an inclusion criterion of the study. 63% of participants with fistulising disease had a single fistula. The Committee considered that as 40 mg once weekly is not a registered dose in New Zealand, only the results for patients receiving 40 mg every other week was relevant to this application. Of this group, 37% showed complete healing at week 56 compared with 13% of the placebo group. The 33% in the adalimumab arm that had achieved healing by week 26 maintained this result through to week 56 and developed no new fistulae. Participant withdrawal during this time left 21 in the adalimumab every other week group at 56 weeks. Adalimumab showed a rapid response in some patients with separation in the rate of closure between the treatment and placebo groups evident from week 2 and statistically significant at week 16.

- 11.6 The Committee considered the open label extension study (ADHERE) published by Colombel et al. (Gut 2009;58:940-948) which followed 38 patients with fistulising disease for an additional year. Patients received adalimumab every other week unless they had previously received open label weekly dosing prior to the extension study or if required due to flare or non-response. Fistulae were assessed for spontaneous drainage or drainage with gentle compression at each study visit. Complete fistula healing was defined as the absence of drainage under both these circumstances. The authors reported that 90% of patients maintained fistula healing over the 12 months of the extension period, however this drops to 74% using a non-responder imputation analysis as seven of the 38 patients withdrew from the study. The Committee noted that previous and concurrent therapies did not appear to influence outcomes however this was difficult to interpret due to the small patient group. The Committee considered that adalimumab resulted in an increased number of significant adverse events.
- 11.7 The Committee considered a double blind randomised placebo controlled trial (ACCENT II) to evaluate the efficacy of infliximab maintenance therapy in 306 patients with fistulising disease (Sands et al. N Engl J Med 2004;350:876-85) which was provided as a comparison to the adalimumab studies. Patients with a response to infliximab induction of at least 50% from baseline in the number of draining fistulae were randomised to receive placebo or infliximab (5 mg/kg) every eight weeks for one year. The primary endpoint was the time to loss of response among patients who had a response at week 14 (n=195). The mean time for loss of response was 14 weeks in the placebo group and 40 weeks in the infliximab group. At week 54, 23% of patients in the placebo group still had a response, compared with 46% of patients in the infliximab group (p=0.001).
- 11.8 The Committee considered that the differences in the patient populations, small patient numbers and different primary endpoints made an indirect comparison between the adalimumab and infliximab studies difficult to perform. However, the Committee considered that it was reasonable to conclude that adalimumab and infliximab have similar effects in patients with fistulising Crohn's disease.
- 11.9 The Committee considered that the strength and quality of the evidence provided was moderate. In addition to the small patient numbers with fistulising disease in the subgroups analysed, the Committee considered that the participants in the CHARM and ADHERE studies had a minimum CDAI score of 220, and therefore may not be

representative of the fistulising disease population being considered for funding in this application.

- 11.10 The Committee considered the current treatments for fistulising Crohn's disease (CD) includes antibiotics, immunomodulators, placement of seton sutures and eventually surgery. The Committee considered the evidence provided by Crohn's and Colitis New Zealand in support of the supplier's application which estimates that success of these treatments in achieving fistula closure is approximately 20%.
- 11.11 The Committee considered the treatment algorithm proposed by the supplier was not supported by recommendations from international guidelines, all of which require previous treatment with alternative therapies which may include antibiotics, immunomodulators and surgery. The Committee considered that the Australian Pharmaceutical Benefits Advisory Committees' (PBAC) recommendations for patients to have trialed 'adequate conventional treatment (defined as at least 4 months therapy with an adequate dose of thiopurine or methotrexate)' would be appropriate.
- 11.12 The Committee considered the Special Authority criteria should involve an objective assessment of fistula(e) in order to measure response to treatment. The Committee considered the renewal criteria used by PBAC to be reasonable, which requires a reduction in the number of open draining fistulae from baseline by at least 50% and/or a marked reduction in drainage of all fistula(e) from baseline, together with less pain and induration as reported by the patient, and continuing treatment until patients had achieved complete fistula(e) healing. The Committee noted that the fistula grading tool used by PBAC may be useful in assessing response to treatment.
- 11.13 The Committee considered that potential patient numbers who would be targeted by the proposed criteria in New Zealand could be extrapolated from the retrospective study conducted in Australia by Burger et al (MJA 2010;192:375-377). Patients with CD and perianal CD for whom anti-TNF alpha treatment was clinically indicated were assessed to determine whether they satisfied the Australian criteria for subsidised treatment between 2004 and 2008. The authors reported that approximately 30% of patients with fistulising CD who would benefit from anti-TNF alpha treatment did not qualify for funding. This corresponds to approximately 2% of the total number of CD patients assessed. The Committee noted that accordingly, in New Zealand the number of patients likely to benefit from funded treatment would be approximately 200.

Part II: Review of TNF inhibitor Special Authority criteria for severe chronic plaque psoriasis and Crohn's disease

Application

- 11.14 The Committee reviewed information from PHARMAC staff and clinicians in relation to the Special Authority criteria for adalimumab (Humira) for Crohn's disease and severe chronic plaque psoriasis, and for etanercept (Enbrel) for severe chronic plaque psoriasis, in Section B of the Pharmaceutical Schedule.

Recommendation

- 11.15 The Committee **recommended** that no changes be made either to the current initial or renewal Special Authority criteria for adalimumab (Humira) for Crohn's disease and severe chronic plaque psoriasis or to the current initial or renewal Special Authority criteria for etanercept (Enbrel) for severe chronic plaque psoriasis.

Discussion

- 11.16 The Committee noted that the tumour necrosis factor (TNF) alpha inhibitor Special Authority criteria for the rheumatology-related indications (juvenile idiopathic arthritis, rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis) were recently reviewed by the Rheumatology Subcommittee of PTAC, and that PHARMAC staff were seeking a similar review from PTAC for the remaining funded indications (severe chronic plaque psoriasis and Crohn's disease).

Severe chronic plaque psoriasis (adalimumab and etanercept)

- 11.17 The Committee noted that some dermatologists had requested that criterion 2.1.1 ("Patient has "whole body" severe chronic plaque psoriasis with a Psoriasis Area and Severity Index (PASI) score of greater than 15, where lesions have been present for at least 6 months from the time of initial diagnosis") be amended to reduce the PASI cutoff from 15 to 12."
- 11.18 The Committee agreed with the dermatologists' view that this would result in more patients accessing treatment; however, the Committee considered that the use of adalimumab or etanercept in these patients was unlikely to represent a cost-effective use of health funds, given that the cost-effectiveness under the current criteria was already relatively poor.
- 11.19 The Committee noted that in the pivotal clinical trials of TNF inhibitors in patients with severe chronic plaque psoriasis the mean PASI score of participants ranged between 18.4 and 20.2 with standard deviations of 6.7 to 7.5 (CHAMPION (Adalimumab) PASI 20.2 +/- 7.5 (Saurat JH. Stingl et al British Journal of Dermatology. 2008; 158:558-66; REVEAL (Adalimumab) PASI 19 +/- 7.08 (Menter A et al. J Am Acad Dermatol 2008;58:106-15; Etanercept PASI 18.4 +/- 6.7 (Leonardi, C et al. N Engl J Med 2003; 349:2014-2022). The Committee noted that a PASI of 15 would cover most of the worst affected participants included in the studies, which it felt was a reasonable balance of access versus cost.
- 11.20 The Committee considered that, taking into account the available evidence, cost and cost-effectiveness of adalimumab and etanercept in chronic severe plaque psoriasis, a cutoff of "greater than 15" in criterion 2.1.1 was reasonable and should remain.
- 11.21 The Committee noted that criterion 2.1.1 is not the only criterion via which patients with psoriasis can currently access treatment with TNF inhibitors as there is an alternative criterion 2.1.2 ("Patient has severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot, where the plaque or plaques have been present for at least 6 months from the time of initial diagnosis").

- 11.22 The Committee reviewed the remainder of the initial and renewal criteria for severe chronic plaque psoriasis and considered that there was no need to make any changes to any of these criteria at this time.

Crohn's disease (adalimumab)

- 11.23 The Committee noted that PHARMAC had received recent requests from clinicians to amend the renewal criteria to allow weekly 40 mg adalimumab dosing for patients with Crohn's disease, in particular for patients who were losing efficacy on fortnightly 40 mg dosing or experiencing disease flare.
- 11.24 The Committee noted that it had previously considered this issue at its February 2010 meeting and had recommended that weekly 40 mg dosing be specifically excluded from the adalimumab Special Authority criteria for all funded indications, with the exception of patients with rheumatoid arthritis not taking concomitant methotrexate who have received inadequate benefit from fortnightly 40 mg administration.
- 11.25 The Committee noted that the only new supporting evidence provided was a publication (Sandborn et al. *Inflamm Bowel Dis* 2011;17:141-151) of data from the CHARM trial that the Committee had previously reviewed in poster form at its February 2010 meeting. In this publication, of 260 patients who were randomised to 12 weeks of fortnightly adalimumab in CHARM, 120 (46%) subsequently moved to open-label adalimumab due to lack of response, loss of response or disease flare. Of these, 49 continued fortnightly administration and 71 moved to weekly administration; 36 completed the trial on weekly adalimumab. Of 71 patients on weekly adalimumab, therapy, 37% achieved Crohn's Disease Activity Index (CDAI) <150, 58% achieved a decrease in CDAI of ≥ 100 points and 63% achieved a decrease in CDAI of ≥ 70 points.
- 11.26 The Committee considered that the results of this trial were difficult to interpret due to small patient numbers, unblinded administration and high drop-out rates. In addition, due to the reactive nature of the study there was no evidence available on comparative outcomes for participants who had a disease flare and were either maintained on fortnightly dosing or moved to weekly dosing. The study also did not allow for reducing back to fortnightly dosing once control was achieved so there are no data on this aspect.
- 11.27 The Committee noted that the trial data suggest that up to 14% of patients with Crohn's disease starting on adalimumab would end up on weekly dosing were this permitted under funding rules. The Committee considered that this figure could be higher in New Zealand if weekly 40 mg dosing was permitted, as patients who did not meet the renewal criteria on fortnightly 40 mg dosing would likely try weekly 40 mg dosing in an attempt to boost efficacy and meet the renewal criteria. The Committee considered that this could result in such patients accessing up to a year of extra treatment – at double the usual dose and, consequently, extremely poor cost-effectiveness.
- 11.28 Taking into account the available evidence, cost, and cost-effectiveness of adalimumab, the Committee considered that criterion 3 in the renewal criteria, which specifies that adalimumab is to be administered at doses no greater than 40 mg every 14 days, should not be amended.

- 11.29 The Committee reviewed the remainder of the initial and renewal criteria for Crohn's disease and considered that there was no need to make any changes to any of these criteria at this time.
- 11.30 The Committee noted that in a separate agenda item at this meeting it had made a recommendation to alter the Special Authority criteria for adalimumab for Crohn's disease; however, it was noted that that recommendation was to add new criteria to cover an additional patient group rather than to alter any of the existing criteria.

Part III: Clarification of August 2011 PTAC minute for ustekinumab (Stelara) for severe chronic plaque psoriasis

- 11.31 The Committee noted advice from PHARMAC that its previous recommendation regarding ustekinumab and that a limit of two biologic therapies be included as part of a Special Authority, was not possible under the current claims system. The Committee considered that this recommendation remained clinically appropriate but noted that as this was not possible to implement this should not be considered a reason not to list ustekinumab.

12 Riluzole for amyotrophic lateral sclerosis

Application

- 12.1 The Committee reviewed an updated proposal from Sanofi Aventis New Zealand Limited in support of its application to list riluzole (Rilutek) on the Pharmaceutical Schedule for the treatment of amyotrophic lateral sclerosis (ALS), as well as an updated cost-utility analysis (CUA) performed by PHARMAC staff.

Recommendation

- 12.2 The Committee **recommended** that riluzole be funded for patients with ALS, subject to the following Special Authority criteria, with a medium priority. The Committee considered that these criteria should be reviewed by the Neurology Subcommittee of PTAC prior to funding.

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

All of the following

1. patient has amyotrophic lateral sclerosis with disease duration of 5 years or less; and
2. patient has at least 60 percent of predicted forced vital capacity within 2 months prior to the initial application; and
3. Either
 - 3.1. All of the following:
 - 3.1.1. the patient is ambulatory; and
 - 3.1.2. have not undergone tracheostomy; and
 - 3.1.3. have not experienced respiratory failure;

OR

- 3.2. All of the following
 - 3.2.1. are not ambulatory; and
 - 3.2.2. have not undergone tracheostomy; and
 - 3.2.3. have not experienced respiratory failure; and

3.2.4. are either able to use upper limbs or able to swallow.

Renewal application from relevant specialist. Approvals valid for 18 months for applications meeting the following criteria:

Either

1. All of the following:
 - 1.1. are ambulatory, and
 - 1.2. have not undergone tracheostomy, and
 - 1.3. have not experienced respiratory failure;
2. All of the following:
 - 2.1. are not ambulatory, and
 - 2.2. have not undergone tracheostomy, and
 - 2.3. have not experienced respiratory failure, and
 - 2.4. are either able to use upper limbs or able to swallow.

12.3 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*.

Discussion

- 12.4 The Committee noted that it had reviewed an application from Sanofi-Aventis for the listing of riluzole (Rilutek) for amyotrophic lateral sclerosis (ALS) at its meetings in August 2009 and August 2010. Both times PTAC had recommended that the application be declined, because of its poor efficacy, high cost and poor cost-effectiveness.
- 12.5 The Committee considered that the evidence previously reviewed suggested that treatment with riluzole improves survival by approximately 2 to 3 months and may delay the need for a tracheostomy by approximately the same amount of time. The Committee considered that non-invasive ventilation (NIV) is preferred to tracheostomy in most New Zealand centres.
- 12.6 The Committee considered a publication by Bourke et al (Lancet 2006;5:140-7) which studied the effects of NIV on survival and quality of life in 92 patients with ALS. Patients received either NIV or standard care and most received riluzole (86% of NIV group and 89% of standard care group). In addition to survival, primary outcome measures were the time maintained above 75% of baseline and the mean improvement in the short form 36 mental component summary (SF36 MCS) and the sleep apnoea quality of life index (SAQLI). The authors reported that NIV significantly improved median survival by 48 days ($p=0.0062$) and quality of life measures. In a subgroup analysis of patients with good bulbar function, the NIV group showed a median survival benefit of 205 days ($p=0.006$) compared with standard care, and quality of life was maintained for most of this period. NIV improved some quality of life indices including the mean improvement in SAQLI ($p=0.018$) but conferred no survival benefit in the subgroup of patients with poor bulbar function. The authors concluded that NIV improves survival with maintenance of, and improvement in, quality of life in patients with ALS who do not have severe bulbar involvement, and that the survival benefit from NIV in this group is much greater than that from currently available neuroprotective therapy.

- 12.7 The Committee considered a publication by Qureshi et al (Amyotrophic Lateral Sclerosis 2009;10:324-31) which assessed the developments in clinical care for ALS over the last two decades. The authors performed an analysis on patients in the placebo arms of three randomised treatment efficacy trials recently conducted by the Northeast ALS Consortium (NEALS). Survival and rates of progression were assessed. A systematic literature review was also conducted of clinical trials in ALS between 1994 and 2008 and the data from the placebo arms of 12 trials were reported. In the three NEALS trials, survival improved over time in the placebo cohort (p=0.05); however, the rate of functional decline, including muscle and respiratory strength, did not change over time. The review supported these results. The authors concluded that improved survival is related to improvements over time in symptomatic care for patients with ALS.
- 12.8 The Committee considered that these two publications supported the benefits of modern supportive care for patients with ALS and indicate that treatment with riluzole would infer a small additional health gain.
- 12.9 The Committee noted that the CUA result and budget impact analysis for riluzole in the ALS patient group proposed by the supplier had improved significantly following the supplier's recent proposal and subsequent update of the model.
- 12.10 The Committee noted the updated CUA from PHARMAC staff, which had been revised to reflect the new price in the supplier's proposal. The Committee noted that PHARMAC staff were seeking further advice from PTAC regarding the quality of life of patients with ALS into the model. The Committee noted that the health state of patients with end-stage ALS is variable and depends largely on bulbar involvement, due to NIV being suitable or not. The Committee considered that the utility values proposed for quality of life (approximately 0.3 based on NZ EQ-5D scores) that lead to a QALY gain per patient of approximately 0.06 (for an additional 2-3 months survival) to be fair.
- 12.11 The Committee considered that riluzole may be more cost-effective if targeted to patients with severe bulbar involvement as there are few other treatment options for these patients and NIV is less effective in these patients.

13 Saxagliptin for Type II diabetes mellitus

Application

- 13.1 The Committee reviewed an application from Astra Zeneca to list saxagliptin (Onglyza) on the Pharmaceutical Schedule for the treatment of patients with type 2 diabetes.

Recommendation

- 13.2 The Committee **recommended** that saxagliptin is listed on the Pharmaceutical Schedule for the treatment of patients with type 2 diabetes with a low priority.
- 13.3 The Committee referred the consideration of which DPP-4 inhibitor should be considered for funding to the Diabetes Subcommittee.
- 13.4 The Committee **recommended** that Special Authority criteria should apply and referred the consideration of this to the Diabetes Subcommittee.

- 13.5 The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (ii) *The particular health needs of Māori and Pacific peoples;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

Discussion

- 13.6 The Committee considered the evidence supplied in the application. The Committee considered the randomised, four arm, placebo controlled, double blind study by Rosenstock et al. (Curr Med Res Opin. 2009; 25: 2401-2411) of the effect of saxagliptin monotherapy (2.5 mg, 5 mg, or 10 mg daily) in 401 treatment-naïve patients with type 2 diabetes. Two hundred and sixty five patients completed 24 weeks of the study protocol. The primary endpoint was the change in HbA1c from baseline. The reduction in HbA1c for all saxagliptin doses was statistically significant compared with placebo ($p < 0.0001$). The mean change in HbA1c for each group was: saxagliptin 2.5 mg 7.9% vs 7.5%, saxagliptin 5 mg 8.0% vs 7.5%, saxagliptin 10 mg 7.9% vs 7.3% and placebo 7.9% vs 8.15%. Weight loss occurred in all treatment groups including placebo. The rate of adverse events was similar between saxagliptin and placebo with sinusitis. Infective adverse events were among the most commonly reported adverse events including upper respiratory tract and urinary tract infections, sinusitis and nasopharyngitis. The Committee considered that as patients were treatment naïve, it was uncertain how relevant this trial was in supporting the use of saxagliptin in New Zealand given that it is likely to be used second or third line.
- 13.7 The Committee considered a 24 week randomised, double blind, placebo controlled study of saxagliptin (2.5 mg, 5 mg and 10 mg) or placebo plus a stable dose of metformin (1500-2500 mg) in 743 patients with an HbA1c of ≥ 7.0 and $\leq 10.0\%$ (DeFronzo et al. Diabetes care, 2009; 32: 1649-1655). The primary endpoint of the study was change in HbA1c from baseline. All doses of saxagliptin resulted in statistically significant reductions in HbA1c compared with placebo; 2.5 mg -0.59%, 5mg -0.69%, 10 mg -0.58% vs placebo +0.13%. 74.3% of patients receiving saxagliptin had an adverse event vs 64.8% of the placebo group. Incidences of hypoglycaemic adverse events were similar in the saxagliptin and placebo groups. The Committee noted the high withdrawal rate from this study due to poor glycaemic control or requiring rescue treatment.
- 13.8 The Committee considered a multicentre, randomised, double blind study (Jadzinsky et al. Diabetes, Obesity and Metabolism 2009;11:611-622) where saxagliptin was given in combination with metformin as initial therapy in 1306 treatment naïve patients with type 2 diabetes. Patients receiving combination treatment reported statistically significant reductions adjusted mean decreases in HbA1c when compared with monotherapy. The reduction in HbA1c from baseline, reported after 24 weeks was approximately -2% for patients taking metformin alone, -1.7% for patients taking saxagliptin 10 mg daily alone and -2.5% both groups receiving combination therapy of metformin and either saxagliptin 5 mg or 10 mg. The Committee noted a subgroup analysis showed that the reduction in HbA1c was greatest for patients with high baseline levels.

- 13.9 The Committee considered (Goke et al. *Int J Clin Pract* 2010;12:1619-1631), a 52 week non-inferiority study in which saxagliptin was compared with glipizide as add on therapy to metformin. 858 patients who were receiving at least 1.5 g metformin daily were randomised to receive either saxagliptin 5 mg or glipizide 5 mg titrated to 20 mg daily in addition. At 24 weeks, the adjusted mean change in HbA1c from baseline for the saxagliptin and glipizide groups was -0.74% and 0.80% respectively. Patients receiving saxagliptin had a significantly smaller proportion of hypoglycaemic events than patients receiving glipizide (3.0% vs 36.3%; $p < 0.0001$) and a divergent impact on body weight was reported (adjusted mean change from baseline -1.1 kg saxagliptin vs 1.1 kg with glipizide; $p < 0.0001$). The Committee noted that in this population of patients with mild type 2 diabetes taking metformin, the addition of either saxagliptin or glipizide has a modest impact on HbA1c reduction.
- 13.10 The Committee considered a 24 week multicentre, randomised, double blind, three-arm safety and efficacy study (Chacra et al. *Int J Clin Pract* 2009;63:1395-1406) and its 52 week extension study (Chacra et al. *Diab Vasc Dis Res* 2011;8:150) of saxagliptin 2.5 mg or 5 mg in combination with a suboptimal 7.5 mg dose of glyburide (a sulphonylurea) versus up-titrated glyburide to 15 mg. The authors reported the adjusted mean changes from baseline HbA1c for saxagliptin 2.5 mg, saxagliptin 5 mg and up-titrated glyburide after week 24 were -0.6%, -0.7% and +0.05% respectively. The Committee noted that a slight increase from baseline in body weight occurred in all patient groups, however the mean increases were significantly greater in the saxagliptin treatment groups compared with patients receiving glyburide alone. The Committee noted that the HbA1c improvements were not sustained at 76 weeks as reported in the extension study, with the mean changes from baseline reported to be +0.11% (2.5 mg saxagliptin), +0.03% (5 mg saxagliptin) and +0.69% (glyburide) respectively.
- 13.11 The Committee considered a systematic assessment of cardiovascular outcomes in eight phase two and three trials evaluating saxagliptin in patients with type 2 diabetes (Frederich et al. *Postgrad Med* 2010; 122:16-27). From a total of 4607 patients who were randomised and treated, 3356 received saxagliptin and 1251 received a comparator treatment (metformin, placebo or up-titrated glyburide). Sixty one patients had a cardiovascular event, 1.1% of those were taking saxagliptin and 1.8% received a comparator (relative risk, 95% CI, 0.44, (0.24-0.82)).
- 13.12 The Committee considered a retrospective analysis of the risk of bladder cancer in patients from the Kaiser Permanente Northern California diabetes registry who were 40 years of age or older between 1997 and 2002 and receiving pioglitazone (Lewis et al. *Diabetes Care* 2011;34:916-922). Overall, the author reported that ever use of pioglitazone was not associated with risk of bladder cancer (hazard ratio 1.2 (95% CI 0.9-1.5)). In a sub analysis of patients receiving pioglitazone for longer than 24 months an increased risk was reported. The hazard ratio for >24 months therapy was 1.4 (1.03-2.0) and >48 months therapy was 1.7 (1.1-2.9).
- 13.13 The Committee considered the evidence to support the application was of modest strength and quality and all were sponsored by pharmaceutical companies.
- 13.14 The Committee considered that saxagliptin is similar in efficacy to pioglitazone with both pharmaceuticals reducing HbA1c by 0.5% on average. The Committee noted that metformin and sulphonylureas remain the most effective oral treatments. The

Committee considered that saxagliptin has a low risk of hypoglycaemia and weight gain, and may offer cardiovascular benefits. The Committee noted saxagliptin interacts with other medicines also metabolised by the same cytochrome P450 pathway, and that dose reduction is necessary in patients with moderate to severe renal dysfunction. The Committee noted that long term data on the risks of treatment with saxagliptin is lacking.

- 13.15 The Committee considered that saxagliptin would be used in combination therapy with metformin, a sulphonylurea and/or insulin and is likely to replace pioglitazone in the current treatment algorithm.
- 13.16 The Committee noted that the patient numbers provided by the supplier were an underestimate of the potential patient population. The Committee considered that uptake would be similar to that observed for pioglitazone when funding was made available which correlates to approximately 200 to 250 patients per month.
- 13.17 The Committee considered that restrictions should be placed on access to treatment in order to target patients who would gain the most benefit - a cost-utility analysis would help to determine this. The Committee noted that the cost of treatment for DPP-4 inhibitors is high in comparison to other oral hypoglycaemic treatments and is comparable to the cost of insulin. The Committee noted that if DPP-4 inhibitors were used in combination with insulin, the costs would be even greater.
- 13.18 The Committee considered that potentially a DPP-4 inhibitor should be made available for patients who are not able to meet their HbA1c target without serious hypoglycaemic episodes following an adequate trial of currently funded treatment. The Committee recommended that the Diabetes Subcommittee review the available DPP-4 inhibitors and GLP-1 agonists in New Zealand, provide its opinion and develop targeted Special Authority criteria.

14 Tocilizumab (Actemra) for the Treatment of Rheumatoid Arthritis and Systemic Juvenile Idiopathic Arthritis

Application

- 14.1 The Committee reviewed an application from Roche Products (NZ) Ltd for the funding of tocilizumab (Actemra) on the Pharmaceutical Schedule for the treatment of patients with rheumatoid arthritis (RA) following tumour necrosis factor (TNF)-alpha inhibitor failure and for the treatment of patients with systemic juvenile idiopathic arthritis (sJIA).

Recommendation

- 14.2 The Committee **recommended** that tocilizumab should be funded for the treatment of RA subject to access criteria restricting its use to patients who have not responded to prior treatment with standard disease modifying antirheumatic drugs (DMARDs) and at least one TNF inhibitor, with a low priority.
- 14.3 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.

- 14.4 The Committee further **recommended** that tocilizumab should be funded for the treatment of sJIA subject to access criteria (with clear stopping criteria) restricting its use to patients who have not responded to prior treatment with non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX) and systemic corticosteroids, with a high priority, subject to Medsafe registration of tocilizumab for sJIA and, preferably, PTAC review of published data from the TENDER trial.
- 14.5 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (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: Rheumatoid Arthritis

- 14.6 The Committee noted that tocilizumab is a monoclonal antibody to interleukin (IL)-6 receptors which is administered in-hospital as a 1-hour intravenous infusion, and that the purpose of the review was to consider whether or not tocilizumab should be included as part of a national preferred medicines list (PML) for DHB hospitals which was currently being established by PHARMAC.
- 14.7 The Committee noted that the supplier had provided a large body of evidence in support of the use of tocilizumab in RA, including ten randomised controlled trial publications and several meta-analyses and extension studies.
- 14.8 The Committee noted that a 2011 Cochrane Systematic Review (Singh et al. J Rheumatol 2011;38:10-20) included eight of the ten randomised controlled trials (Choy et al. Arthritis Rheum 2002;46:3143-50; Emery et al. Ann Rheum Dis 2008;67:1516-1523; Genovese et al. Arthritis Rheum 2008;58:2968-2980; Maini et al. Arthritis Rheum 2006;54:2817-2829; Nishimoto et al. Arthritis Rheum 2004;50:1761-1769; Nishimoto et al. Ann Rheum Dis 2007;66:1162-1167; Nishimoto et al. Mod Rheumatol 2009;19:12-19; Smolen et al. Lancet 2008;371:987-97). In seven of the studies, patients had active RA despite prior treatment with MTX or DMARDs. In one study (Emery et al. 2008) patients had had inadequate response to one or more TNF inhibitors. The trials had similar summary descriptions of participants: 80% female, mean age 50–60 years, baseline Disease Activity Score (DAS) of approximately 6.5 (where reported) and duration of RA of over 8 years except Nishimoto et al. 2009 in which patients had a mean disease duration of approximately 2 years. The randomised treatment duration was between 12 and 24 weeks for most studies, except for Nishimoto et al. 2009 which was 52 weeks. Tocilizumab was given at doses of 4 mg/kg or 8 mg/kg every 4 weeks.

- 14.9 The Committee noted that the authors of the Cochrane analysis reported a risk ratio (RR) for achieving American College of Rheumatology (ACR) 20 for the four studies comparing tocilizumab 8 mg/kg every 4 weeks plus DMARD versus DMARD alone of 2.5 (1.9–3.4) at weeks 16–24. Weaknesses of the studies identified by the authors were limited sample size, short follow-up, lack of safety outcomes, lack of head to head comparisons with other biologics, and lack of reporting of allocation concealment.
- 14.10 An additional randomised controlled trial compared tocilizumab plus MTX with MTX alone in patients who had received an inadequate response to MTX, and reported higher response rates for ACR20 at week 24 in tocilizumab 8 mg/kg recipients compared with MTX alone (Kremer et al, *Arthritis Rheum* 2011;63:609-621).
- 14.11 Overall, the Committee considered that there is strong, high-quality evidence that tocilizumab 8 mg/kg every 4 weeks plus MTX/DMARDs provides better outcomes than MTX/DMARDs in patients with active RA. However, the Committee noted that most of the studies were of relatively short duration (in the context of the duration of RA) and longer-term follow-up data are not yet mature.
- 14.12 The Committee considered that, although there are no head-to-head studies against other biologics, the indirect comparison analysis reported by Bergman et al (*Semin Arthritis Rheum* 2010;39:425-441) suggests that tocilizumab provides similar efficacy to other biologics in patients with RA refractory to DMARDs.
- 14.13 The Committee considered that the results of Emery et al. (*Ann Rheum Dis* 2008;67:1516-1523) supported the efficacy of tocilizumab in combination with MTX in patients who had previously received an inadequate response from TNF inhibitors, with an ACR20 response rate of 43% at 16 weeks versus 11% in patients receiving MTX alone. The Committee noted that this response rate is about half that reported in other tocilizumab studies (ACR20 range at follow-up of between 60% and 80%). The Committee noted that there were no trials of tocilizumab in patients who had tried other biologics (e.g. rituximab).
- 14.14 The Committee considered that tocilizumab would likely be taken in combination with MTX (with or without other DMARDs); however, the Committee noted that the results of the randomised controlled trial reported by Jones et al. (*Ann Rheum Dis* 2010;69:88-96), in which tocilizumab monotherapy was compared with MTX in patients in whom treatment with MTX or biologic agents had not previously failed, supported the efficacy of tocilizumab monotherapy (8 mg/kg every 4 weeks) compared with MTX in patients with RA, with a higher ACR20 response reported in the tocilizumab group at week 24 compared with MTX (70% vs 53%, respectively).
- 14.15 The Committee noted that an analysis of the adverse events in six of the trials reported an increase in frequency of adverse events for tocilizumab versus control, RR 1.5 (1.3–1.9) (Campbell et al, *Rheumatology* 2011;50:552-62). In two analyses of longer-term data (median treatment duration of 3.8 years and 3.6 years), tocilizumab was associated with a serious infection rate of 6.2 per 100 patient years and 5 per 100 years, respectively (Nishimoto et al. *Mod Rheumatol* 2010;20:222-232; Genovese et al. *Ann Rheum Dis* 2011;70(Suppl3):609 [abstract]), which is similar to that seen with other biologics. Between 0.2% and 0.5% of patients experienced anaphylaxis; other side effects included an increased risk of abnormal liver function tests, neutropenia and

altered lipid profile with increased cholesterol. The Committee considered that the data were not mature enough to evaluate the cancer risk.

- 14.16 The Committee considered that patients on tocilizumab would likely require lipid monitoring in addition to the usual monitoring requirements for patients on biologics (e.g. infection screening and monitoring for malignancy), and the infusions and associated adverse events (infusion reactions and anaphylaxis) would also require additional resources.
- 14.17 The Committee noted that there are two funded community biologic treatments (the TNF inhibitors adalimumab and etanercept) for patients with severe, active RA refractory to DMARDs. The Committee considered that there would be a proportion of these patients who would be refractory to TNF inhibitors and who could benefit from another class of biologic agent such as tocilizumab, although efficacy from tocilizumab would likely be lower in these patients (as evidenced by the results of Emery et al. *Ann Rheum Dis* 2008;67:1516-1523). The Committee noted that rituximab was currently a treatment option for these patients in some DHB hospitals; however, access to rituximab was not currently consistent across all DHBs.
- 14.18 The Committee noted that the application had been reviewed by the Ad-hoc Rheumatology Subcommittee at its October 2011 meeting and that the Subcommittee had recommended funding tocilizumab either as a first-line biologic treatment option in patients with RA for whom TNF inhibitors are contraindicated only if it was cost-neutral to the health sector, or as a second- or third-line biologic treatment option (depending on patients' ability to tolerate MTX and the availability of rituximab for RA) with a high priority within the context of the rheumatology therapeutic area.
- 14.19 The Committee considered that, taking into account the cost of tocilizumab at the proposed prices, the fact that it is a hospital-administered product and would have resource implications on DHB hospitals which may limit its use, and the lack of longer-term data, tocilizumab should be funded subject to access criteria restricting its use to patients who have not responded to prior treatment with standard DMARDs and at least one TNF inhibitor.
- 14.20 The Committee considered that if rituximab was also available consistently across the country for this patient group, it could be reasonable to also require a trial of rituximab prior to accessing tocilizumab if tocilizumab was more expensive; however, the Committee noted that there was no evidence in support of the efficacy of tocilizumab following rituximab.

Discussion: Systemic Juvenile Idiopathic Arthritis

- 14.21 The Committee noted that tocilizumab was not currently registered by Medsafe for use in sJIA.
- 14.22 The Committee noted that sJIA is a severe form of JIA and is typically very difficult to treat.
- 14.23 The Committee noted that the supplier had provided only limited published evidence in support of the use of tocilizumab in sJIA, with the key evidence consisting of one randomised controlled trial (Yokota et al. *Lancet* 2008;371:998-1000) and abstract

reports of another ongoing randomised controlled trial (TENDER). Two phase 2 dose-finding studies (Woo et al. *Arthritis Res Ther.* 2005;7(6):R1281-8; Yokota et al. *Arthritis Rheum* 2005;52:818-25) and a number of other abstracts were also provided, along with unpublished data from TENDER.

- 14.24 In the published randomised controlled trial (Yokota et al. 2008), 56 children aged 2–19 years (with disease onset <16 years) with active sJIA despite more than three months' treatment with corticosteroids were given tocilizumab 8 mg/kg every 2 weeks during a 6-week open-label lead-in phase. Forty-three patients achieving an ACR Paediatric (ACR Pedi) 30 response and a CRP <5 mg/L were then randomly assigned to receive placebo (n=23) or to continue tocilizumab (n=20) for 12 weeks. The primary outcome measure was maintenance of ACR Pedi 30 and CRP <5 mg/L, which was achieved by 80% of patients in the tocilizumab group and 17% of patients in the placebo group, RR 4.7. This was followed by an open-label extension to 48 weeks in patients who had responded to tocilizumab and required further treatment; by the end of the open-label extension phase, 90% of patients (43 of 48) achieved ACR Pedi 70 responses. Serious adverse reactions included anaphylactoid reaction, gastrointestinal haemorrhage, bronchitis and gastroenteritis.
- 14.25 In the TENDER trial, 112 children aged 2–17 years (average 10 years) with active sJIA for at least 6 months and an inadequate response to previous NSAIDs and corticosteroids were randomly assigned to receive tocilizumab (n=75) every 2 weeks (8 mg/kg for patients ≥30 kg; 12 mg/kg for patients <30 kg) or placebo (n=37) for 12 weeks. There was an early escape option to tocilizumab taken by 20 patients in the placebo arm (13 at the week 2 visit). Members noted that ACR Pedi 30 and an absence of fever was achieved by 85% of tocilizumab-treated patients and 24% of placebo-treated patients, respectively (De Benedetti et al. *Arthritis Rheum* 2010;62(Suppl 10):1434). One participant experienced angioedema and urticaria and there were two infections, although the denominator was unclear.
- 14.26 The 12-week randomised phase of TENDER was followed by an extension phase in which all patients received open-label tocilizumab. A total of 77 of the 88 patients who had reached 52 weeks of tocilizumab treatment by May 2010 had ACR Pedi 30 plus absence of fever (De Benedetti et al, *Ann Rheum Dis* 2011;70(Suppl 3):67). Fifteen serious infections were observed in patients who had received 52 weeks of treatment by May 2010, 6 of which were considered related to tocilizumab; again, the denominator was unclear. The Committee noted that data to week 104 were now available; however, this had not been provided in the supplier's submission.
- 14.27 Overall, the Committee considered that the strength of the evidence provided was weak to moderate but appeared to support the efficacy of tocilizumab in patients in with sJIA. The Committee noted its concerns around the lack of long-term data for tocilizumab in sJIA.
- 14.28 The Committee noted that the application had been reviewed by the Ad-hoc Rheumatology Subcommittee at its October 2011 meeting and that the Subcommittee had recommended funding of tocilizumab for patients with sJIA as a first-line treatment option (i.e. with no requirement for any prior treatment to be trialled) with a high priority within the context of the rheumatology therapeutic area.

- 14.29 The Committee noted that patients in the randomised controlled trials had received prior treatment with other agents, including corticosteroids, NSAIDs, MTX and biologics. The Committee noted that the review material provided in the supplier's submission suggests that MTX and biologics may not be as effective in sJIA as in other JIA subtypes, and that some patients with sJIA develop a potentially fatal complication – macrophage activation syndrome – where biological agents have been considered both the trigger and treatment. The Committee considered that the evidence supporting this was of low quality.
- 14.30 The Committee considered that the sJIA patient group who would most benefit from tocilizumab would be those who had not responded to prior treatment with NSAIDs, MTX and systemic corticosteroids.
- 14.31 The Committee noted the Ad-hoc Rheumatology's comment that while many children with sJIA ultimately end up being treated with etanercept, this is because their disease progresses and they develop arthritis and so meet the articular criteria for etanercept for JIA (i.e. they are not being treated with etanercept for the systemic features of JIA). The Committee considered that from the available evidence it was not possible to estimate the incremental benefit of tocilizumab over etanercept and that the indirect comparison analysis performed by the supplier suggesting that tocilizumab was superior to infliximab for sJIA was not convincing. In addition, the Committee noted that neither etanercept nor infliximab is registered or funded for use in sJIA in New Zealand. Therefore, the Committee considered that neither etanercept nor infliximab would be an appropriate comparator for tocilizumab in any cost-utility or budget impact analyses performed by PHARMAC staff, although members considered that it was possible that tocilizumab might delay the use of, or prevent the need for, etanercept in some sJIA patients.
- 14.32 The Committee considered that tocilizumab for sJIA would be associated with the same monitoring and resource requirements as tocilizumab for RA.
- 14.33 The Committee noted that the National Institute for Health and Clinical Excellence (NICE) guidance report for tocilizumab for sJIA suggests that the starting age of patients in cost-effectiveness models should be 5 years (not 2 years) to reflect the mean age of children with the disease and to allow for them to have tried and experienced treatment failure with NSAIDs, corticosteroids and MTX. The Committee agreed with this suggestion, noting that it considered that the average age of sJIA patients on tocilizumab treatment if it was funded was likely to be higher than estimated by the supplier.
- 14.34 The Committee considered that if tocilizumab was funded as recommended by the Committee, the patient numbers would likely be substantially higher than those estimated by the supplier (2-12 patients per year), potentially as high as the number of patients currently accessing etanercept via the JIA criteria.