

PTAC meeting held 11 & 12 August 2011

(minutes for web publishing)

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

PTAC may:

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

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- (i) protect the privacy of natural persons (section 9(2)(a));
- (ii) protect information where the making available of the information would be likely to unreasonably prejudice the commercial position of the person who supplied or who is the subject of the information (section 9(2)(b)(ii));
- (iii) protect information which is subject to an obligation of confidence or which any person has been or could be compelled to provide under the authority of any enactment, where the making available of the information would be likely to prejudice the supply of similar information, or information from the same source, and it is in the public interest that such information should continue to be supplied (section 9(2)(ba)(i)); and/or
- (iv) enable PHARMAC to carry on, without prejudice or disadvantage, negotiations (including commercial and industrial negotiations (section 9(2)(j))).

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1 Subcommittee minutes

1.1 Cancer Treatments Subcommittee – 15 April 2011

- 1.1.1 The Committee noted paragraph 3.5.2.3: “33% die in rest homes” and considered that it preferred the term “residential care” to “rest homes”.
- 1.1.2 The Committee noted the Special Authority (SA) criteria for deferasirox in congenital inherited anaemias in paragraph 9.10. The Committee **recommended** that the SA criteria 3.2 be changed from “severe persistent gastrointestinal side effects like vomiting and diarrhoea” to “severe persistent vomiting or diarrhoea”. The Committee also recommended that “arthralgia” be removed from SA criteria 3.3.
- 1.1.3 The remainder of the record of the meeting was noted and accepted.

1.2 Diabetes Subcommittee – 11 July 2011

- 1.2.1 The Committee notes the Special Authority criteria for insulin pumps and **recommended** that dietary compliance criteria be included in the criteria.
- 1.2.2 The Committee reiterated that nocturnal hypoglycaemia was a particularly severe complication of diabetes.
- 1.2.3 The Committee considered that the diabetic groups targeted by the Special Authority criteria were very high users of outpatient and community diabetes services.
- 1.2.4 The remainder of the record of the meeting was noted and accepted.

2 Fluticasone/salmeterol (Seretide) for asthma

Application

- 2.1 The Committee considered [withheld under s 9(2)(a) of the OIA] request for a review of the decisions made at their November 2010 meeting in regard to a two part Application from GlaxoSmithKline New Zealand Limited for the listing of high dose Seretide (250 µg fluticasone / 50 µg salmeterol metered dose inhaler (MDI) or Seretide Accuhaler (500 µg fluticasone / 50 µg salmeterol) for the treatment of asthma and COPD under a Special Authority endorsed by a Specialist and the removal of the requirement for patients to be on individual inhaled corticosteroid (ICS) and long acting beta agonist (LABA) inhalers for three months prior to a prescription of the combination Seretide or Seretide Accuhaler.

Recommendation

- 2.2 The Committee reiterated its **recommendation** from its November 2010 meeting to decline the application to list higher strength fluticasone/salmeterol (Seretide) inhalers on the Pharmaceutical Schedule.

The Decision Criteria particularly relevant to this recommendation are: *(iii)The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv)The clinical benefits and risks of pharmaceuticals;(v)The cost-effectiveness in 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.*

- 2.3 The Committee **recommended** that the priority given to the removal of the three month trial period from the Special Authority pertaining to prescriptions for combination inhaled corticosteroids with Long-acting Beta-Adrenoceptor Agonists be changed from a medium priority to a high priority.

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 in meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi)The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 2.4 The Committee reviewed the previous correspondence with [withheld under s 9(2)(a) of the OIA] regarding decisions made following GSK's application for the listing of high dose fluticasone with salmeterol and the removal of the requirement for patients to be on individual inhaled corticosteroid (ICS) and long acting beta agonist (LABA) inhalers for three months prior to a prescription of the combination Seretide or Seretide Accuhaler
- 2.5 The Committee noted that at their November 2010 meeting the recommendations were to decline the application for high dose Seretide and recommend the removal of the three month trial period from the Special Authority for combination inhalers with a medium priority. The Committee noted that there was some benefit for high dose combination inhalers in asthma and COPD but there were concerns over significant side effects and that if high dose inhaled steroids were warranted such regimens could be achieved by combining existing inhalers. With regard to the three month trial period, the Committee considered it was difficult to justify a period of separate ICS and LABA inhalers given poor adherence and the adverse effects of single LABA therapy.
- 2.6 The Committee noted the papers by Crane et al (Lancet 1989;1(8644):917-22 and Thorax 1995;50Suppl 1:S5-10) and Pearce et al (Lancet 1995;345(8941):41-4). These papers were of historical value examining the relationship between the widespread use of the short-acting beta-agonist fenoterol and an associated increase in deaths from asthma in New Zealand over the same time and concluded that while there may be other factors that had contributed to increased asthma mortality in New Zealand, fenoterol was the probable cause.

- 2.7 The Committee noted two meta-analyses [withheld under s 9(2)(a) of the OIA]. Wijesinghe et al (Eu Respir J 2009;34:803-11) undertook a systematic review that included the AstraZeneca Formoterol Clinical trial Safety database and Novartis Food and Drug administration Formoterol Briefing Document. Randomised, controlled, clinical trials of greater than four weeks duration that compared formoterol (as a separate or combination ICS/LABA inhaler) with a non-LABA comparator treatment in the management of asthma were included. 62 studies with 27,821 subjects randomised to formoterol and 21,506 randomised to non-LABA products were included in the meta-analysis. The main finding was that there was insufficient power to determine the risk of asthma death associated with formoterol treatment. Weatherall et al (Thorax 2010;65:39-43) conducted a meta-analysis of asthma deaths in randomised clinical trials from the GlaxoSmithKline database that compared salmeterol with a non-LABA comparator treatment in asthma. 215 studies with 106,575 patients were in the meta-analysis. There were 35 asthma deaths recorded in these studies, 30 of them arising from two studies. The findings suggested that salmeterol as monotherapy in poorly controlled asthma may increase the risk of asthma mortality, and that this risk is reduced with concomitant ICS therapy. There was no evidence to suggest that combination salmeterol/fluticasone propionate therapy is associated with an increased risk of asthma deaths but recommended further studies to determine this hypothesis.
- 2.8 The Committee noted two perspectives - Kramer (N Engl J Med 2009;360;16:1592-5) and Chowdhury and Dal Pan (N Engl J Med 2010;362:13:1169-71). Commentary by Kramer on the FDA meta-analysis suggested overall odds of harm (combined asthma related deaths, intubations and hospitalisations) amounting to 2.8 for 1,000 patients receiving LABA compared to those not receiving a LABA; 3.6 per 1,000 for those receiving LABA therapy without an ICS compared to those with non-LABA therapy. The recommendation was against using LABA as monotherapy with the emphasis that LABAs should be added to corticosteroids when control with corticosteroids was ineffective. In addition the FDA recommended stopping LABA therapy when asthma is adequately controlled and the use of fixed dose combination products in younger patients to ensure compliance.
- 2.9 The Committee noted that Rodrigo and Castro-Rodriguez (Thorax 2011 April) concluded that LABA monotherapy significantly increased asthma related adverse events. They also concluded that the use of LABA and steroids, preferably in one inhaler, reduced asthma related events. They supported the use of LABA and ICS in a single inhaler.
- 2.10 The Committee noted four observational studies that were included in [withheld under s 9(2)(a) of the OIA] request for review: Stempl DA et al (RespMed 2005;99:1263-1267); Stoloff SW et al (J Allergy Clin Immunol 2004;113:245-251); Suissa S et al (N Eng J Med 2000; 343:332-6) and Williams et al J Allergy Clin Immunol 2004;114(6):1288-93). In Stoloff's study patients on combined inhalers filled 4.06 refills compared to 2.35 refills for separate fluticasone and salmeterol, 2.27 refills for fluticasone alone, 1.83 refills for fluticasone and montelukast and 4.51 for montelukast alone. The authors concluded that a single inhaler containing both an ICS and a LABA might increase the likelihood that patients are getting more optimal ICS therapy. Stoloff's study was of a similar design and reached similar conclusions. Suissa et al calculated that the rate of death from asthma decreased by 21 percent with each additional canister of inhaled corticosteroids used in the previous year and concluded that the regular use of low-dose inhaled corticosteroids is associated with a decreased risk of death. Williams et al concluded that poor asthma outcomes were associated with lower adherence to inhaled corticosteroids. The

Committee noted that these studies were subjected to significant biases but the conclusions are biologically plausible.

- 2.11 The Committee also reviewed the RCT conducted by Perrin and others (Perrin et al, J Allergy Clin Immunol, 2010; 126:505-510) examining adherence to a combined fluticasone salmeterol inhaler or separate inhalers in asthmatic patients. A significant difference in adherence was noted after 6 months. Only a small minority was taking salmeterol alone (4%). The Committee considered that the high rate of adherence could be related to the group of patients studied (they have participated in asthma trials before). The Committee considered that the study may have been underpowered to estimate the difference in adherence. However, the Committee considered this study was the only randomised trial to look at the adherence of LABA and ICS in asthmatics and the results are probably more robust than reported in observational studies.
- 2.12 Several other clinical trials and studies were reviewed and the Committee noted that the balance of evidence provided in the submission suggest that the use of LABAs alone in asthmatics could be harmful. In general the evidence and opinion seem to favour the combination ICS with LABA inhalers and the Committee supported this view. In November 2010 the Committee had recommended that the three month trial period be removed from the special authority for combination inhalers and gave the recommendation a medium priority.
- 2.13 The Committee considered whether funding should be withdrawn from LABA single inhaler therapy in the treatment of asthma. The recommendation was that funding should remain but a prescribing guideline should be added to the listing and Special Authority of LABAs stating that LABA monotherapy should not be used in the treatment of asthma.
- 2.14 The Committee noted that the submission did not provide new evidence for the value of a combined high dose fluticasone with salmeterol inhaler. The Committee noted that the use of high dose steroids has not changed in New Zealand during the past few years. The high dose beclomethasone age equivalent daily dose (BAEDD) had dropped from 984 in 2003 to ~856 µg per day by 2005 and has remained stable. Approximately 200 patients have been prescribed more than 2000 ug BAEDD per day and 35% of these are also on a LABA.
- 2.15 The Committee noted that while there is a need for a high dose ICS with a LABA in some patients with unstable asthma the number of patients is not high. At its November 2010 meeting the Committee considered that the need could be met by using a combination of available inhalers i.e. a combination ICS with LABA plus an ICS. Reasons for not supporting the listing of a high dose ICS with LABA combination included the significant increase in side effects and concern about dose creep. The Committee considered that their original recommendation to decline the application for listing a high dose Seretide should stand.

3 Pregabalin (Lyrica) for neuropathic pain

Application

- 3.1 The Committee reviewed an application from Pfizer for funding of pregabalin (Lyrica and Pfizer Pregabalin) on the Pharmaceutical Schedule for the treatment of refractory peripheral neuropathic pain.

Recommendation

- 3.2 The Committee **recommended** that pregabalin be funded subject to Special Authority criteria for the treatment of refractory peripheral neuropathic pain associated with post herpetic neuralgia or diabetic peripheral neuropathy with a low priority.

The Committee proposed the following Special Authority criteria for pregabalin as a draft and noted that the Special Authority criteria and appropriate treatment sequencing for neuropathic pain should be finalised by the Analgesic Subcommittee:

Initial application – (peripheral neuropathic pain associated with post herpetic neuralgia or diabetic peripheral neuropathy) from any relevant practitioner. Approvals valid for 3 months where the patient has, been unresponsive or unable to tolerate treatment following a reasonable trial with therapeutic doses of (first line agent +/- second line agent)

Renewal – from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

Either:

1. The patient has demonstrated a marked improvement in their pain control (prescriber determined); or
2. The patient has previously demonstrated clinical responsiveness to pregabalin and has now developed neuropathic pain in a new site.
3. Not to be used in combination with gabapentin

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

- 3.3 The Committee considered that peripheral neuropathic pain includes diabetic peripheral neuropathy, post herpetic neuralgia, painful polyneuropathy, post mastectomy pain, phantom limb pain, Guillain-Barre syndrome, neuropathic cancer pain, chemotherapy induced neuropathy, HIV induced neuropathy, complex regional pain syndromes and chronic lumbar root pain.
- 3.4 The Committee considered that current therapies for peripheral neuropathic pain are primarily tricyclic antidepressants (TCAs) and anti-epileptic drugs (e.g. gabapentin, which is funded as a second line treatment in New Zealand for patients who cannot tolerate or who have not received benefit from an adequate trial of TCAs). A recent Cochrane review (Moore et al. Cochrane Database of Systematic Reviews 2011; Issue 3:CD007938) found that gabapentin provided moderate benefit (defined as at least 30%

improvement in pain scores) in 42% of patients and provided good benefit (defined as at least 50% improvement in pain scores) in 31% of patients with peripheral neuropathic pain. More than 50% of patients did not receive significant benefit from gabapentin treatment.

- 3.5 The Committee noted that the International Association for the Study of Pain published measures to assess treatment efficacy in pain treatment trials (Haanpaa M, Attal N, Backonja B et al. NeuPSIG Guidelines on Neuropathic Pain Assessment. Pain 152 (2011) 14-27). These include i) Pain Relief Scales including the visual analogue scale, verbal rating scale and numerical rating score which measure pain at baseline and at endpoint; ii) the Patient Global Impression of Change (PGIC) or similar clinical global impression of change; iii) the proportion of responders getting >50% pain relief (gold standard) or >30% pain relief (clinically meaningful); iv) use of rescue medication; v) short form McGill pain questionnaire and vi) temporal relationship (may be considered).
- 3.6 The Committee considered the four randomised controlled trials (RCTs) supplied with the application (Protocols 196, 1004, 1037 and 1064), all of which have been published.
- 3.7 Protocol 196 (published as van Seventer et al. Curr Med Res Opin 2006;22(2):375-84) was a three phase open label extension study of patients with post herpetic neuralgia. Following baseline measurements, patients were randomised into one of four 12 week treatment arms to take placebo or pregabalin in doses of either 150 mg, 300 mg or 600 mg per day. The primary endpoint was the last recorded weekly mean pain score compared with baseline measurements using the verbal rating scale and the numerical rating scale. The Committee considered that the secondary endpoint which measured the mean sleep interference scores did not provide a clinically meaningful measure of pain relief. The Committee noted that all doses of pregabalin produced statistically significant reduction in pain compared with placebo. However, only the treatment arm receiving 600 mg pregabalin daily reported clinically meaningful pain relief scores (34.6% reduction in mean pain scores from baseline to endpoint). The Committee noted the high withdrawal rate (36.6% of patients withdrew during the double blind treatment phase). For patients on the 600 mg dose 36.7% reported dizziness, 25.6% reported somnolence and 13.3% reported peripheral oedema.
- 3.8 Protocol 1004 (published as Stacey et al. J Pain 2008;9:1006-1017) was a placebo controlled trial which studied the effect of fixed and flexible dosing regimens of pregabalin on allodynia and the time to onset of pain relief in patients with post herpetic neuralgia. The Committee noted that the reporting of primary endpoints differed between the protocol (reduction in pain score) and publication (mean time to achieve pain relief). The Committee considered that mean time to achieve pain relief or the measurement of allodynia were not clinically meaningful measures of pain relief. Other published outcomes were not recorded in the protocol and the Committee considered that little meaningful information could be taken from the trial.
- 3.9 In Protocol 1064 (published as van Seventer et al. Eur J Neurol 2010;17:1082-9), participants suffering from post-traumatic neuropathic pain were randomised to either placebo or a flexible dose regimen of pregabalin (the mean dose was 326 mg per day). The Committee noted the high 19.6% drop out rate in the pregabalin arm compared with 7.1% in the placebo arm with somnolence and dizziness the most commonly reported side effects. The authors reported that pregabalin produced a statistically significant reduction in pain from baseline compared with placebo, however, the Committee

considered that the pregabalin arm did not achieve a 30% or greater reduction in pain scores and therefore this was not a clinically meaningful outcome.

- 3.10 Protocol 1037 (published as Moon et al. Clin Ther 2010;32(14):2370-85) assessed the efficacy and tolerability of pregabalin in Korean patients with peripheral neuropathic pain over ten weeks. Seven percent of participants had diabetic peripheral neuropathy, 61% had post herpetic neuralgia and 32% had post-traumatic peripheral neuropathic pain. The primary measure was the endpoint vs baseline mean pain score and showed that pregabalin was more effective than placebo. However the Committee considered that the reduction in pain was not clinically significant (<30% reduction from baseline).
- 3.11 The Committee considered an additional RCT by Arezzo et al (BMC Neurology 2008;8:33) which studied patients with diabetic peripheral neuropathy and showed that 600 mg pregabalin daily improved pain significantly (44% reduction in pain score from baseline). The difference in pain scores between pregabalin and placebo groups was significant despite the placebo arm also reporting a 27% reduction in pain scores from baseline.
- 3.12 The Committee considered seven non-randomised, non placebo controlled open label trials. Stacey et al (Pain Med 2008;9(8):1202-8) included patients with diabetic peripheral neuropathy or post herpetic neuralgia who were considered refractory to treatment after receiving an unsatisfactory response to at least three prior treatments including gabapentin (doses of 1.8 g per day) and TCAs (amitriptyline greater than 75 mg doses per day). Participants received between 150 mg and 600 mg pregabalin in a flexible dosing regimen for three months then had a treatment holiday of up to 28 days. If patients reported worse pain during the treatment free period, they resumed treatment for a further three months. Patients were allowed to take other treatments during the course of the 18 month observation period including TCAs and gabapentin. The Committee considered that the design of this study was poor and that there were no meaningful data in this trial.
- 3.13 The Committee considered the open-label prospective study published by Freynhagen et al (Int J Clin Pract. 2007;61(12):1989-96) in which patients with refractory, intractable or problematic central or peripheral neuropathic pain received an increasing dose of pregabalin to a mean dose of 356 mg after 28 days. The mean pain score reduction was statistically significant but was not considered by the Committee to be clinically significant (i.e. reduction in pain score was not >30%). The Committee noted that no subgroup analysis was performed therefore the relevance of the results to patients with peripheral neuropathic pain would be difficult to infer from this study.
- 3.14 The Committee considered a cohort study examining the utility of substitution of pregabalin for gabapentin therapy in patients with peripheral neuropathic pain (Toth et al Pain Med. 2010 Mar;11(3):456-65). Patients receiving gabapentin as monotherapy were split into three groups: 77 patients continued to receive gabapentin, and 69 patients switched to an equivalent dose of pregabalin. Of these, 33 patients had been responsive to gabapentin treatment and 36 had not. The Committee noted that the switch was only worthwhile in the group of patients who responded to gabapentin (which would make them ineligible for funded pregabalin under the access criteria proposed by the supplier) and a meaningful reduction in pain was achieved after six months of treatment but was not sustained at 12 months. The Committee noted that the group who were not responsive to gabapentin did not receive a clinically meaningful reduction in pain while

taking pregabalin, however this group did significantly better than patients who took gabapentin throughout.

- 3.15 The Committee noted the post-marketing event monitoring study by Lampl et al (J Neurol. 2010;257:1265-73). Patients either received flexible doses of pregabalin (up to 600 mg daily) as an add-on to current treatments or as monotherapy or they continued their current therapy but with changes to dose and medicine combinations permitted. The study included patients with neuropathic pain, but did not specify whether the pain was central or peripheral in nature. The Committee noted that stopping current treatment and switching to fixed or flexible dosing of pregabalin was only slightly more effective than continuing and modifying doses of existing treatments and both arms showed clinically meaningful pain reduction.
- 3.16 Three unpublished studies submitted as posters were provided by the supplier in support of the Application. The Committee considered the evidence provided in the Hanu-Cernat 2005 study was of little value as 75% of participants in the trial did not have a confirmed diagnosis of neuropathic pain. Douglas et al 2008 and Allen 2005 both reported meaningful pain score reductions over the course of the studies in small groups of patients refractory to gabapentin and or TCAs.
- 3.17 The Committee considered that the evidence supplied in the application was of modest to moderate strength and of variable quality and the submission from the supplier was poor. The Committee noted that the evidence was strongest for patients with post herpetic neuralgia due to much higher numbers of patients within the trials. Although there were a smaller number of patients with diabetic peripheral neuropathy within the trials the Committee noted that pregabalin treatment may benefit patients with diabetic peripheral neuropathy. The Committee noted that on the basis of the evidence presented, pregabalin may be reasonably effective at high doses (600 mg per day) however high doses would likely be associated with marked increases in somnolence and dizziness.
- 3.18 The Committee noted that there are few effective treatments for neuropathic pain and this is reflected by poor response rates in the reviewed trials. The Committee considered that there is a clear need for an effective treatment.
- 3.19 The Committee considered that pregabalin would be of most benefit in patients with post herpetic neuralgia or diabetic peripheral neuropathy with good renal function (creatinine clearance >30 ml/min). The Committee considered that there was little evidence to support the use of pregabalin in other pain modalities. The Committee further considered that correct targeting of pregabalin would require accurate diagnosis of post herpetic neuralgia or diabetic peripheral neuropathy and that treatment for conditions such as fibromyalgia would not be evidence based. The Committee considered that the evidence did not support long-term treatment with pregabalin.
- 3.20 The Committee considered that pregabalin has a similar effect to gabapentin, although there have been no head to head trials. The Committee noted that pregabalin has a faster onset of action when compared with gabapentin. The Committee considered that the risks of treatment with pregabalin would be similar to those for gabapentin – somnolence, dizziness and weight gain.

- 3.21 The Committee considered that there was little evidence to support the use of pregabalin as an add-on therapy or in combination with other treatments and doing so would increase the risk of side effects such as somnolence, dizziness and potentially increase the risk of falls.
- 3.22 Given the higher rates of diabetes in Maori/Pacific people the Committee noted that this population may be more likely to suffer from diabetic peripheral neuropathy and, therefore, could benefit more from pregabalin treatment than the population as a whole.
- 3.23 The Committee considered that the number of patients with peripheral neuropathic pain who are likely to try pregabalin following unsuccessful treatment with a TCA then gabapentin could be approximately 20%. However, the Committee considered that there may be an inclination for clinicians to try pregabalin early without adequate trials of the maximum tolerated dose of TCAs then gabapentin; therefore the estimate of patient numbers could be low.
- 3.24 The Committee noted that there is little evidence to suggest that pregabalin would be effective in patients who do not respond to gabapentin and therefore would not recommend it as third line in the current treatment algorithm. The Committee noted that the appropriate position for pregabalin in relation to other treatments for neuropathic pain should be considered by the Analgesic Subcommittee.
- 3.25 The Committee considered that van Seventer et al. (Curr Med Res Opin 2006; 22(2): 375-84)) and Arezzo et al (BMC Neurology 2008, 8:33) would be the most useful evidence to model efficacy in any cost utility analysis for pregabalin in patients with post herpetic neuralgia and diabetic peripheral neuropathy, respectively. The Committee considered that 600 mg per day should be used in any analysis as this was the only dose to achieve clinically meaningful reduction in pain scores in the clinical trials.

4 Imiglucerase (Cerezyme) widening access for Gauchers disease

Application

- 4.1 The Committee considered the proposed Special Authority criteria drafted by the Gaucher Disease Panel to widen access to imiglucerase for the treatment of Gaucher Disease in children.

Recommendation

- 4.2 The Committee **recommended** that the Special Authority be widened and clarified in the Pharmaceutical Schedule with high priority as described below.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals.; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 4.3 The Committee considered the clinical manifestations of Gaucher Disease (GD) in the lung, spleen, liver and bone marrow are a major cause of morbidity. There are three types of GD. Type 1, or non-neuronopathic is the commonest (90%) and presents in the first two decades with progressive deterioration, those who present earlier in life tend to have more severe disease. Morbidity is due to amongst other things visceromegaly, thrombocytopenia, anaemia, growth retardation, osteopenia, osteosclerosis, osteonecrosis, and painful bone crises. Type 2, or acute neuronopathic, is fatal in the first two years of life. Finally type 3, is a heterogeneous group of conditions with variable neurological complications and a more protracted course.
- 4.4 The Committee considered the paediatric presentations of GD described in the literature. Kaplan et al. (*Arch Pediatr Adolesc Med.* 2006;160:603-608) described the clinical findings at diagnosis in 877 paediatric patients. At diagnosis 81% had radiological evidence of bone disease, 27% reported bone pain, 9% were having a bone crisis (bone crisis is defined as acute onset pain which requires immobilisation and narcotics for pain relief), 34% <5th centile for height. Non-skeletal findings at diagnosis included: 40% being anaemic, 49% having platelets <120, with 9% severely thrombocytopenic (<60), 96% splenomegaly (defined as >5xN), 87% hepatomegaly (defined as 1.25xN), with 16% >2.5xN.
- 4.5 The Committee noted the paper by Rossi et al. (*Joint Bone Spine*, 2011; 78: 70–74) which described the clinical features in 44 paediatric patients from the French Lysosomal Disease Centre, particularly detailing bone findings at diagnosis. The proportion of skeletal and non-skeletal disease at diagnosis was broadly similar in this cohort to the earlier larger study by Kaplan et al.
- 4.6 The Committee noted that imiglucerase, a recombinant form of the deficient enzyme, is funded in New Zealand via the Gaucher Panel. Currently, imiglucerase is approved in New Zealand for type one disease at a dose of 15iu/kg/month under agreed criteria, given as fortnightly intravenous infusions. Currently there are 18 patients funded in New Zealand, 16 with type 1 disease, and two with type 3 disease. Seven of the 18 patients receive 30 iu/kg/month (of whom three are children).
- 4.7 The Committee noted that New Zealand uses lower doses of imiglucerase than other countries. The Committee noted that some authors recommend starting doses for children of at least 120iu/kg/month and up to 240iu/kg/month in type 3 disease (Baldellou et al. *Eur J Ped* 2004; 163: 67-75, Davies et al. *J Inherit Metab Dis* 2007; 30:768–782), attributing the higher dose requirement (and caution in dose reduction) to the rapid skeletal changes in childhood and the need to develop a competent skeleton.
- 4.8 The Committee considered a commentary published by Zimran (*Blood* 2011, prepublished online June 13 2011; DOI 10.1182/blood-2011-04-308890) based on imiglucerase treatment protocols in Israel, which applies limits to the doses used due to the large number of GD patients (the prevalence of GD in Ashkenazi Jews being one in 850). The Committee noted the author's comments that the recommended starting dose of imiglucerase is 30iu/kg/month and up to 60iu/kg/month in children but ultimately the dosage of imiglucerase remains controversial as no overriding authority has evidence-based data to resolve the issue.

- 4.9 The Committee considered the proportion of paediatric patients who would be eligible for starting treatment at a dose of 30iu/kg/month. The Committee noted that the Kaplan et al. (Arch Pediatr Adolesc Med. 2006;160:603-608) paper suggests that the majority of paediatric GD patients have radiological evidence of bone disease at diagnosis. While not all of these patients would be started at 30iu/kg/month according to the proposed criteria, others would also have at least three of the other clinical criteria. The Committee considered about 25% of patients or less would start at 15iu/kg/month (all others would meet the criteria to begin treatment on 30iu/kg/month and that the initial criteria proposed by the Gaucher panel were appropriate).
- 4.10 The Committee considered that reasonable definitions are reflected in the proposed criteria to measure dose increase, decrease or treatment withdrawal. The Committee noted that while parameters such as haematologic counts and visceral organ size can be easily measured, bone marrow sequelae are not so easily measured and take longer to show change. The Committee noted that the key markers are bone MRI abnormalities and serum chitotriosidase levels and these are measured at appropriate intervals in the proposed access criteria, however it considered that the hepatomegaly criterion should be stated in multiples of normal volume and not as 5cm below costal margin (>2.5xN would be appropriate).
- 4.11 The Committee considered that the dosage renewal criteria for 30iu/kg/month should also reflect symptomatic and clinical objective improvements in clinical parameters rather than just being secondary measures and therefore should be the similar to the 15iu/kg/month renewal criteria. The Committee considered that the compliance criteria resulting in possible stoppage should apply to both doses.
- 4.12 The Committee considered that the timeframes reflected in the proposed criteria (one year for haematological indices and visceral size, and two years for bone pathology) are appropriate and pragmatic to allow the effect of treatment to be observed and that the proposed monitoring frequency is appropriate.
- 4.13 The Committee recommended that an upper age of 18 or the attainment of radiological evidence of skeletal maturity (which ever is later) be added to the Special Authority criteria to define and differentiate child and adult patients.
- 4.14 The Committee considered that the 15iu/kg/month renewal criteria are essentially an individual treatment plan where patients are assessed based on the main symptoms for which therapy was initiated. The Committee recommended that the 30iu/kg/month renewal criteria should be changed, so that if increasing to the 30iu/kg/month dose is started due to bone crisis or abnormalities then these become the renewal criteria on which treatment success is judged, and that if increasing to the 30iu/kg/month dose is started for three or more clinical parameters then this in turn becomes the renewal criteria on which treatment success is judged.
- 4.15 The Committee recommended that the compliance stopping criteria should be the same for both doses of imiglucerase.
- 4.16 The Committee considered that the dose decrease criteria for patients receiving 30iu/kg/month should constitute stopping criteria. The Committee noted that if patients continue to deteriorate or show no improvement while receiving 30iu/kg/month, they would be unlikely show any greater response to 15iu/kg/month. The Committee noted

that patients with bone symptoms may require a longer period of treatment to show improvements and the criteria allows the Gaucher Panel to assess patients on an individual case basis.

- 4.17 The Special Authority criteria follow (additions are in bold, deletions in strikethrough and PTAC changes are in highlight):

ELIGIBILITY CRITERIA FOR IMIGLUCERASE

~~ACCESS CRITERIA FOR TREATMENT WITH IMIGLUCERASE (CEREZYME)~~

~~ELIGIBILITY CRITERIA FOR IMIGLUCERASE FUNDING~~

These guidelines are intended to assist relevant practitioners in gauging which patients are likely to be approved for imiglucerase. In view of the complexity of Gaucher disease severity assessment, each application is thoroughly evaluated by the Gaucher Panel to determine the appropriate imiglucerase treatment.

All requested studies should be carried out in line with the relevant professional guidelines. Patients with Gaucher disease who meet the following criteria may be eligible for initiation of imiglucerase treatment based on current clinical evidence.

Schedule 1: Guidelines for use of imiglucerase

Patients eligible for initial approval of Special Authority

1. The **patient must have a** diagnosis of symptomatic type 1 **or type 3** Gaucher disease ~~must have been established~~ by the demonstration of:

- Specific deficiency of glucocerebrosidase in leukocytes or cultured skin fibroblasts; and
- Genotypic analysis

Histology and genotype tests to be supplied with the initial application once available. Baseline MRI whole body Short Tau Inversion Recovery (STIR) and serum chitotriosidase reports must be provided.

2. **Patients who have Gaucher type 2 disease are not eligible for subsidised treatment.** If a patient has a medical condition which significantly impacts on life expectancy or the treatment would not have a significant chance of causing an improvement in the patient's condition, it is considered inappropriate to initiate therapy with imiglucerase.
3. ~~Animal reproductive studies have not been conducted with imiglucerase. It is also not known whether imiglucerase can cause foetal harm when administered to a pregnant woman, or can affect reproductive capacity. Imiglucerase should be given to a pregnant woman only where the perceived benefits outweigh the potential risks.~~
4. Patients who receive government funded imiglucerase treatment must be willing to participate in the long term evaluation of the efficacy of the treatment, as approved, if necessary, by an ethics committee. Collated data collected may be made available to international investigators. Patient anonymity should be preserved.
5. Unless otherwise agreed by PHARMAC, imiglucerase shall not be subsidised at a dose exceeding ~~45~~ **30** iu/kg/month rounded to the nearest whole vial.
6. The **Gaucher** Panel will consider applications and provide advice on the appropriate management of any other patients referred to it by PHARMAC.

Criteria for Commencement of Treatment

Initial Treatment criteria

Imiglucerase 15 iu/kg/month

One of the following clinical parameters would be severe enough to cause symptoms and as such are considered sufficient to warrant therapy **with imiglucerase 15 iu/kg/month**.

Imiglucerase 30 iu/kg/month for children*

Any three of the following clinical parameters, or bone crisis, or severe/significant bone marrow abnormalities on MRI would indicate severe disease and warrant initial therapy with imiglucerase 30 iu/kg/month. Unless there are exceptional circumstances only children are eligible for a starting dose of 30 iu/kg/month.

Haematological complications:

1. Haemoglobin <95g/l, after other causes of anaemia, such as iron deficiency have been treated or ruled out, or severe symptoms from anaemia at a higher level of haemoglobin.
2. Thrombocytopenia < 50 x 10E9/L on two separate occasions at least one month apart.
3. Bleeding complications associated with thrombocytopaenia, irrespective of the platelet count.
4. At least two episodes of severely symptomatic splenic infarcts confirmed by CT or other imaging of the abdomen.
5. Massive symptomatic splenomegaly.

Skeletal complications:

1. One acute bone crisis severe enough to require hospitalisation and or major pain management strategies.
2. Radiographical MRI evidence of incipient destruction of any major joint, such as the hips or shoulder.
3. Spontaneous fractures or vertebral collapse.
4. Chronic bone pain not controlled by the administration of non-narcotic analgesics or anti-inflammatory drugs, or requiring continuous medication or causing a significant loss of time from work or school.

Hepatic complications:

1. Evidence of significant liver dysfunction, such as incipient portal hypertension, attributable to Gaucher disease (treatment should start before this stage is reached).
2. Significant hepatomegaly e.g., **5 cms below the right costal margin >2.5 times the normal liver volume** or significant abnormality of the liver function tests.

Pulmonary complications:

Reduced vital capacity from clinically significant or progressive pulmonary disease due to Gaucher disease.

Systemic complications

Growth failure in children: significant decrease in percentile linear growth over a 6-12 month period.

Test reports, including MRI whole body STIR, serum chitotriosidase and haematological data, must accompany the initial application.

'Children' can be defined by an upper age of 18 or the attainment of radiological evidence of skeletal maturity (which ever is latter).

Patients eligible for renewal of Special Authority

Renewal applications must be submitted to the Gaucher Panel for an annual review.

Criteria for Cessation of Treatment

Renewal of imiglucerase treatment - 15/iu/kg/month

- a) In the event that the Panel determines by some measurable method (for example of a patient refuses on **more than three > 3** occasions to have injection, or loses product) that the patient has failed to comply adequately with the treatment or measures to evaluate the effectiveness of the therapy, the Panel is to:
 - (i) notify PHARMAC of its concerns in respect of that patient; and
 - (ii) make a recommendation to PHARMAC regarding whether funding of imiglucerase for that patients should be withdrawn, and if not, the period and specific conditions under which the Panel would recommend continuance of funding for treatment.
- b) If the patient has demonstrated a symptomatic improvement or no deterioration in the main symptom for which therapy was initiated as set out below:

- bleeding abnormalities;
- chronic fatigue;
- gastro intestinal complaints;
- bone pain; or
- psychosocial function,

combined with clinically objective improvement or no deterioration in haemoglobin levels, platelet counts and liver and spleen size, then treatment should be continued.

e) The results of treatment will be re-evaluated every 12 months by the Panel. If there has been no significant response to treatment after 12 months (visceral or haematological), Imiglucerase will be discontinued. Bony changes may require a longer period of treatment and cases will be assessed on an individual basis by the panel.

d) In the event of a severe drug reaction treatment may have to be discontinued earlier.

Renewal of imiglucerase treatment - 30iu/kg/month:

Success Criteria

Success of the trial imiglucerase treatment at 30 iu/kg/month will be based on improvements, or no deterioration **in the symptoms for which treatment was initiated.**

Primary success measures

- Radiological (MRI) signs of bone activity performed one year and then two years after treatment begins. At two years there needs to be no deterioration shown by the MRI, compared with MRI taken immediately prior to commencement of therapy increased dose; and
- serum chitotriosidase levels show a decrease (preferably of 10%) compared with level taken immediately prior to commencement of increased dose. Serum chitotriosidase levels during treatment are to be taken at least at 6 month intervals.

Secondary measures (to be assessed for monitoring, but not markers of exit)

- Visceral and haematological indices (haemoglobin levels, platelet counts, bleeding episodes associated with thrombocytopaenia at any level, liver size, liver function tests, spleen size, episodes of splenic infarction, pulmonary vital capacity); and/or
- frequency and/or severity of acute bone crises, radiographic signs of incipient major joint destruction, spontaneous fractures or vertebral collapse; and/or
- systemic complications (namely growth failure); and/or
- the main symptom(s) for which therapy was initiated +/- increased bleeding abnormalities; chronic fatigue; gastro intestinal complaints; bone pain (chronic bone pain not controlled by the administration of non-narcotic analgesics or anti-inflammatory drugs, or requiring continuous medication or causing a significant loss of time from work or school); or psychosocial function.

Schedule 2: Access Criteria for Treatment with Higher Doses of Imiglucerase (Cerezyme) (30 iu/kg/month)

Dose Increase Criteria for children

Should the Panel consider that a patient meets the following criteria, the Panel may make a recommendation to PHARMAC for access to treatment with a higher dose of imiglucerase for that patient. Any decision regarding funding of an increased dose will be made by the PHARMAC Board.

Indications for recommending higher dose

Eligibility criteria for children who have not responded or show poor improvement on 15 iu/kg/month. Clinicians may apply for an increased dose of up to 30 iu/kg/month, rounded to the nearest whole vial. Test results for the following clinical markers, including a repeat MRI whole body STIR and repeat serum chitotriosidase levels must be provided.

Patients are on standard imiglucerase treatment (15 iu/kg/month) and adhering to treatment, and either:

- (Earlier stage) objective indications of lack of improvement +/- incipient clinical deterioration:
 - MRI signs of persistent ongoing or increased bone activity; and

- (ii) Persistent significantly elevated serum chitotriosidase levels; or
 - (iii) Failure to demonstrate a decline in serum chitotriosidase levels and/or:
- b) (Later stage) deterioration in other laboratory and radiological measures of visceral, haematological or skeletal deterioration (haemoglobin levels, platelet counts, hepatomegaly, liver function tests, splenomegaly, radiological signs of pathological fracture joint destruction), and/or:
 - c) (Later stage) frank symptomatic deterioration in main initiating symptoms (bleeding abnormalities; chronic fatigue; gastro intestinal complaints; bone pain, osteonecrotic sequelae, etc.)

The during treatment serum chitotriosidase levels are to be taken at least 6 monthly, and an MRI performed at 12 and 24 months after beginning new treatment dose.

Dose stopping criteria for all patients

- a) In the event that the Panel determines by some measurable method (for example of a patient refuses on **more than three** ≥ 3 occasions to have injection, or loses product) that the patient has failed to comply adequately with the treatment or measures to evaluate the effectiveness of the therapy, the Panel is to :
 - (i) notify PHARMAC of its concerns in respect of that patient; and
 - (ii) make a recommendation to PHARMAC regarding whether funding of imiglucerase for that patients should be withdrawn, and if not, the period and specific conditions under which the Panel would recommend continuance of funding for treatment.
- b) In the event of a severe drug reaction treatment may have to be discontinued **earlier**.
- c) If there has been no significant response to treatment at 15iu/kg/month or 30iu/kg/month after 12 months (visceral or haematological), Imiglucerase will be discontinued. (Bony changes may require a longer period of treatment and cases will be assessed on an individual basis by the panel).

5 Varenicline (Champix) for smoking cessation

Application

- 5.1 The Committee reviewed an update from PHARMAC staff regarding recent safety data for varenicline (Champix) relating to psychiatric effects and cardiovascular risk.

Recommendation

- 5.2 The Committee **recommended** that the safety of varenicline be reviewed again at PTAC's November 2011 meeting following the September 2011 review of varenicline by Medsafe's Medicines Adverse Reactions Committee.

Discussion

- 5.3 The Committee noted that it had previously had significant concerns about the safety of varenicline, and that its February 2009 recommendation to fund varenicline was made in the context of the known risk:benefit profile at the time, the fact that varenicline was in the Intensive Medicines Monitoring Programme (IMMP) and that varenicline would be funded subject to Special Authority criteria designed to ensure varenicline was not used as a first-line treatment and to minimise the safety risks.

- 5.4 The Committee noted that varenicline has been funded since November 2010 subject to Special Authority criteria similar to those proposed by PTAC. The Committee noted that usage of varenicline to date has been considerably higher than estimated.
- 5.5 The Committee noted that varenicline is due to be removed from IMMP from July 2012 due to lack of ongoing funding from Medsafe.
- 5.6 The Committee noted that since it last reviewed varenicline in February 2009 a further 589 post-marketing adverse psychiatric events reported to the United States Food and Drug Administration (FDA), including 150 completed suicides, had been reported. In addition, a number of recent publications have raised the possibility that varenicline is associated with an increased risk of cardiovascular adverse events in patients with existing cardiovascular disease.
- 5.7 The Committee did not accept the suggestion by the supplier (Pfizer) that the psychiatric events were a result of people stopping smoking rather than an adverse effect of varenicline. Members noted that smoking cessation was generally not considered to be a suicide risk factor and other smoking cessation strategies did not seem to carry this risk.
- 5.8 The Committee considered that arguments that the safety risks of varenicline were less than those associated with smoking were ill-founded, as there are three other available smoking cessation treatments (nicotine replacement therapy [NRT], bupropion and nortriptyline) that do not carry the same safety risk as varenicline. The Committee noted that varenicline had shown only small additional benefits over NRT in clinical trials.
- 5.9 The Committee noted that the initial studies on varenicline excluded patients with cardiovascular disease, which is not unusual in clinical trials of this nature. However, a study reported in 2010 (Rigotti et al. *Circulation* 2010;121:221-229) included patients with cardiovascular disease. This was a multicentre, randomised, double-blind, placebo-controlled study in patients aged 35 to 70 years with stable cardiovascular disease. Patients were given varenicline or placebo for 12 weeks. The primary outcome measure was the 4-week continuous abstinence rate (CAR) during the last four weeks of study drug treatment (weeks 9 to 12). The key secondary outcome measure was the CAR from week 9 through 52; other outcome measures included the CAR for weeks 9 to 24, the 7-day point prevalence of tobacco abstinence at weeks 12 (end of drug treatment), 24, and 52 and serious adverse events. Reported or observed cardiovascular events or deaths resulting from any cause were reviewed separately, including nonfatal or fatal myocardial infarction, hospital admission for chest pain, hospitalization for angina pectoris, need for coronary revascularization, resuscitated cardiac arrest, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, new diagnosis of or admission for a procedure to treat peripheral vascular disease, and death resulting from any cause.
- 5.10 The CAR during weeks 9 to 12 was significantly higher in the varenicline group (47.0%) compared with the placebo group (13.9%). Similarly, the CAR for weeks 9 to 52 was significantly higher for varenicline (19.2%) compared with placebo (7.2%). Serious adverse events occurred in 6.5% of patients in the varenicline group and 6.0% of patients in the placebo group. There were no significant differences between the varenicline and placebo groups with respect to cardiovascular mortality, all-cause mortality or serious adverse events. A total of 9.6% of patients in the varenicline group

discontinued treatment due to adverse events, compared with 4.3% of those in the placebo group.

- 5.11 The Committee noted that the authors of this trial concluded that varenicline is effective and well tolerated in patients with cardiovascular disease and that varenicline did not increase cardiovascular events or mortality in this patient population. However, the FDA had been concerned about certain cardiovascular events that were reported in more patients treated with varenicline than those treated with placebo in this trial, including angina pectoris, nonfatal myocardial infarction, need for coronary revascularization and new diagnosis of peripheral vascular disease or admission for a procedure for the treatment of peripheral vascular disease.
- 5.12 The Committee noted that the trial was not designed to have statistical power to detect differences between the arms on the safety endpoints. The Committee considered that it was difficult to assess the cardiovascular risk of varenicline in patients with cardiovascular disease using the results of this trial.
- 5.13 The Committee reviewed a systematic review and meta-analysis of the risk of serious adverse cardiovascular events associated with varenicline (Singh et al. CMAJ 2011;Jul 4). Fourteen trials were included in the meta-analysis, including 8216 patients (4908 varenicline, 3308 placebo). All were placebo-controlled, but varenicline doses differed in the different trials, as did study duration (7 to 52 weeks). Patients with unstable cardiovascular disease were excluded in all trials and some trials excluded patients with any history of cardiovascular disease. The primary outcome measure of the meta-analysis was any ischaemic or arrhythmic adverse cardiovascular event reported during the double-blind period of the trial. A total of 52 (1.06%) of varenicline recipients and 27 (0.82%) placebo recipients had a serious cardiovascular event. This difference was determined to be statistically significant.
- 5.14 The Committee noted that there were a number of limitations with the meta-analysis and that the increased cardiovascular risk, if real, appears to be very small. The Committee noted that Medsafe's Medicines Adverse Reactions Committee would be reviewing the varenicline cardiovascular safety data at its next meeting in early September 2011.
- 5.15 The Committee considered that the safety signals relating to adverse psychiatric events are real and are growing stronger. The Committee noted its significant concerns around the ongoing funding of varenicline given the available safety data, in particular in relation to the adverse psychiatric events.

6 Ketamine (Ketalar) for intractable cancer pain inadequately controlled by opioid analgesics

Application

- 6.1 The Committee reviewed an Application from the Palliative Care Medications Working Group (PCMWG, a Subcommittee of the Ministry of Health's Palliative Care Working Party) for the listing of ketamine on the Pharmaceutical Schedule for use in palliative

care (primarily intractable cancer pain). The Committee also reviewed other information relating to the use of ketamine in intractable pain provided by PHARMAC staff, including information relating to applications to Hospital Exceptional Circumstances.

Recommendations

- 6.2 The Committee **recommended** that the Application for the use of ketamine in intractable cancer pain be declined on the basis of absence of evidence of benefit over placebo.

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.*

- 6.3 The Committee further **recommended** that the randomised controlled trial of ketamine burst therapy led by Professor Janet Hardy in Australia be brought back to the Committee for review once it has been published in a peer-reviewed journal.

Discussion

- 6.4 The Committee noted that ketamine is only registered in New Zealand for use as an anaesthetic agent and that usage of ketamine in the indication for which funding is sought would be off-label.
- 6.5 The Committee noted that the analgesic effect of ketamine is thought to be due to blockade of the N-methyl-d-aspartate (NMDA) receptor. With ongoing painful stimuli the NMDA receptor can become activated and heighten responsiveness to painful stimuli even after the stimulus has ceased, with the result that greater doses of opioids may be required for pain control. In theory, the use of an NMDA receptor antagonist could inhibit the heightened responsiveness to pain and help restore opioid sensitivity. Thus, it has been postulated that ketamine may be useful in sub-anaesthetic doses as “burst therapy” to treat refractory neuropathic, inflammatory or ischaemic pain. In addition, some clinicians consider that higher doses of ketamine (approaching anaesthetic doses) may be useful for treating terminal, uncontrolled, overwhelming pain.
- 6.6 The Committee noted that ketamine can produce psychomimetic effects characterised by hallucinations, confusion, delirium and a feeling of detachment from the body. Other adverse effects include local skin reactions from subcutaneous use, cardiac excitability, excess salivation and increased bowel transit. It is also a potent vasodilator, increasing blood flow by about 60%, and is contraindicated in patients with raised intracranial pressure and severe cardiac disease.
- 6.7 The Committee noted that ketamine is used as an analgesic in the palliative care setting in patients whose pain is no longer responsive to opioid analgesics, usually morphine, oxycodone, fentanyl and methadone. The Committee considered that most patients in this setting would receive ketamine as continuous subcutaneous infusion (CSCI) burst therapy over three to five days at a starting dose of 100 mg/24 hours increasing daily as required by increments of 100 mg/24 hours up to a maximum of 500 mg/24 hours. The

Committee noted that, as evidenced by Hospital Exceptional Circumstances (HEC) applications, in some instances ketamine may be used as longer-term CSCI at doses of 50–500 mg/24 hours for several months.

- 6.8 The Committee noted that the Analgesic Subcommittee of PTAC has reviewed the use of ketamine burst therapy on a number of occasions, most recently in April 2010 when it deferred making a funding recommendation pending availability of results of an ongoing clinical trial in Australia.
- 6.9 The Committee noted that the PCMWG had provided a number of publications in support of the funding of CSCI ketamine for intractable cancer pain. The Committee considered that the best available evidence for CSCI ketamine in the indication sought was from the retrospective and prospective audits, an open-label study sourced by PHARMAC staff, and the recently completed, but as yet only published in abstract form, Australian randomised controlled trial, discussed in the following paragraphs.
- 6.10 Fitzgibbon and Viola (J Palliat Med 2005;8:49-57) reported on a retrospective chart audit of 16 patients with cancer-related pain uncontrolled on opiates and other analgesics. Patients were treated with longer-term CSCI ketamine starting at 50–100 mg/24 hours increasing as needed to a maximum of 700 mg/24 hours. The mean duration of ketamine was 27.4 days (maximum 120 days) and the mean dose was 197 mg/24 hours (maximum 768 mg/24 hours). Pain scores were reduced by at least four out of 10 on a Verbal Rating Scale (VRS) in 94% of patients and breakthrough opioid dose was reduced by at least 50% in 75% of patients. Two patients discontinued due to adverse events.
- 6.11 Jackson et al (J Pain Symptom Manage 2001;22:834-42) reported on a prospective, multicentre, open-label audit of 39 patients who received ketamine burst therapy given as a CSCI over three to five days. The initial dose of 100 mg/24 hours was escalated if required to 300 mg/24 hours or 500 mg/24 hours (the maximum dose). Response was defined as a 50% or greater reduction in mean pain VRS, supported by a corresponding change in at least one of: a 50% or greater reduction in opioid dose, a 50% or greater reduction in the number of opioid breakthrough doses or documented improvement in mobility or functional status. The overall response rate was 67% (29/43). Twenty four of the 29 responders maintained good pain control with a maximum documented duration of eight weeks. This included five patients with mucositis whose condition was felt to be self-limiting. Five of the 29 responders experienced a recurrence of pain within 24 hours, all of whom were re-treated; three remained on ketamine until their death and two had alternative analgesic interventions. Five responders had concurrent interventions which may have influenced their response. Six patients (15%) were able to reduce their opioid dose and 14 patients had increased mobility and function. Significant psychomimetic adverse events occurred in 12 patients.
- 6.12 Jackson et al (J Palliat Care 2010;26:176-83) reported on a multicentre, open-label study of adjuvant ketamine burst therapy over three to five days in 44 palliative care patients with cancer-related pain refractory to opioids and other analgesics. Ketamine was given as CSCI infusion with the dose escalated from a starting dose of 100 mg/24 hours to 300 or 500 mg/24 hours if required. Usual medications were continued; opioid dose reduction and use of breakthrough opioids were permitted. Response was defined as complete pain relief or 50% or greater reduction in mean pain VRS supported by 50% or greater reduction in maintenance opioid dose and/or 50% or greater reduction in number of

breakthrough doses and/or improvement of at least one grade on Eastern Cooperative Oncology Group (ECOG) performance status or improvement of at least one grade on National Cancer Institute (NCI) dysphagia/odynophagia scale for mucositis patient. The response rate was 50%, with 9% of patients becoming pain-free. Seventy-seven percent of responders required 300 mg or more/24 hours with 41% needing 500 mg/24 hours. Twenty three percent of patients achieved an opioid dose reduction. A total of 52 adverse events were recorded: 26 in responders and 26 in non-responders. All grade 3 and 4 toxicities occurred in patients requiring 300 mg or more/24 hours; the most frequent grade 3 toxicity was injection site toxicity and the most frequent grade 4 toxicity was hallucinations. Three responders were re-treated with ketamine at 4–8 weekly intervals; all responded to re-treatment.

- 6.13 The recently completed Australian trial, which has been reported at conferences and in abstract form (e.g. Hardy et al. Support Care Cancer 2011;19(Suppl 2): S170), was a randomised, double-blind, placebo-controlled, multi-site study of CSCI ketamine burst therapy in the management of cancer pain in 185 randomised patients. Patients had chronic uncontrolled cancer pain and a Brief Pain Inventory (BPI) score of three or more. Usual medications including opioids and breakthrough analgesia were continued. Patients were randomised to either ketamine or placebo delivered as CSCI at a dose titrated from 100 to 500 mg/24 hours, according to response and toxicity. Response was defined as a reduction in BPI score by at least two points from baseline after 24 hours with four or less breakthrough doses of analgesia. The primary endpoint was the average BPI score at the start of day six. Secondary endpoints included adverse events, response at days two to five and quality of life. The primary intention to treat analysis found a high placebo response rate (28%) with no significant difference between active and placebo arms ($p=0.78$). The authors concluded that the results do not support the role of CSCI ketamine in the treatment of cancer pain.
- 6.14 Overall, the Committee considered that the strength and quality of the available evidence was weak for burst ketamine and lacking for longer-term CSCI. For burst therapy, the only randomised controlled trial is unpublished and all the other studies are open-label, audits, case studies and communications with inherent biases (e.g. observer bias, reporting bias). In these trials, the lack of placebo control means that the extent of response to ketamine cannot be reliably assessed. In addition, in some of the studies other interventions or medications may have contributed to the analgesic response.
- 6.15 The Committee considered that there were no funded treatments that could be considered similar to ketamine injection and, therefore, it was not possible to estimate dose comparisons with existing treatments.
- 6.16 The Committee considered that ketamine would be used primarily as an add-on treatment in palliative care, noting that midazolam is sometimes given with ketamine to reduce the psychomimetic adverse effects. The Committee considered that it was possible that ketamine could allow opioid dose reduction in some patients, with trials of burst therapy achieving opioid dose reductions of between 15% and 23%, although the extent of the reduction is uncertain given the limitations with the available evidence.
- 6.17 The Committee considered that there were no current problems with access to alternative analgesic treatments for palliative care since there are many options funded without restrictions, although the options become limited with severe intractable opioid-resistant cancer pain.

- 6.18 The Committee noted that Maori and Pacific Island peoples have specific cultural palliative care needs and poorer access to palliative care services compared with the population as a whole. The Committee noted that more Maori (53%) and Pacific Island (42%) peoples die at home compared to the general population (31%).
- 6.19 The Committee considered that the use of CSCI ketamine could be associated with a small increase in nursing costs associated with administration and an increase in costs associated with treating adverse events. Conversely, if the treatment was effective it could result in fewer hospital and hospice admissions for pain control.
- 6.20 The Committee considered that the Analgesic Subcommittee's estimate of 100–150 patients per year taking ketamine burst therapy if it was funded was reasonable. The Committee considered that a proportion of these patients would require repeated courses of burst therapy or longer-term CSCI. The Committee noted that there were approximately 17 requests per year for longer-term CSCI from DHB hospitals through HEC, although this figure would not include hospice use.
- 6.21 The Committee considered that it would be reasonable to use both the PCMWG protocol (100 to 200 to 300 mg/24 hours over 3–5 days) and the trial protocols (100 to 300 to 500 mg/24 hours over 3–5 days) in any financial or cost-effectiveness analyses of burst therapy, which would need to take into account responders and non-responders. The Committee considered that longer-term CSCI ketamine use would typically be for about two months (range one to three months) at doses of approximately 200 mg/24 hours.
- 6.22 Overall, however, the Committee considered that there was insufficient evidence to recommend funding ketamine in the community at this time and look forward to reviewing the published peer-reviewed journal version of the randomised controlled trial of ketamine burst therapy led by Professor Janet Hardy in Australia.

7 Prasugrel for stent thrombosis

Application

- 7.1 The Committee reviewed a PHARMAC staff proposal in relation to the use of ticlopidine in clopidogrel allergy and the cost-utility analysis for second-line prasugrel use in patients who have developed stent thrombosis whilst on clopidogrel.

Recommendation

- 7.2 The Committee **recommended** that prasugrel be listed in the Pharmaceutical Schedule for patients undergoing percutaneous coronary intervention (PCI) who are allergic to clopidogrel and patients who developed stent thrombosis whilst on clopidogrel with a low priority.

The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* and (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

Ticlopidine and prasugrel clopidogrel-allergy

- 7.3 The Committee noted that at its August 2010 meeting, it had considered that ticlopidine would be a reasonable alternative for patients undergoing PCI who were allergic to clopidogrel. The Committee had noted that although ticlopidine was associated with a 2.3% rate of neutropenia, there was a lack of evidence to support the use of prasugrel in this situation. The Committee noted that the Cardiovascular Subcommittee at its October 2010 meeting considered that ticlopidine should not be used as an alternative in this patient group for two reasons: (1) there is no trial evidence to support the use of ticlopidine in drug-eluting stents (DES) and (2) ticlopidine was associated with significant haematological side-effects.
- 7.4 The Committee reviewed clinical trials of ticlopidine in DES and noted that they were mostly observational registry-based studies. Ishakawa et al (Journal of Cardiology 2009; 54: 238-244) showed early definite stent thrombosis (EDST) in 0.21% of patients for ticlopidine in a retrospective cohort of 1885 patients receiving DES and ticlopidine. This appears lower when compared to prasugrel (0.7%) and clopidogrel (1.9%) in DES in the TRITON-TIMI study (Wiviott et al. N Engl J Med 2007; 357: 2001-15) but this was an indirect comparison. In an observational study involving 324 patients who received DES with bifurcation lesions, Kozuma et al (Circ J. 2011 Feb; 75(2): 306-14) found that there was a major adverse cardiac events (MACE) rate of 18.3% at three years compared to 10% for prasugrel and 12% for clopidogrel at 15 months in the TRITON-TIMI trial (Wiviott et al. N Engl J Med 2007; 357: 2001-15). There were, however, no details on other inclusion and exclusion criteria other than lesion types. The committee noted bifurcation lesions are associated with poorer outcomes post stenting. The Committee reviewed other clinical trials involving ticlopidine and clopidogrel use in DES - Park et al (N Engl J Med. 2003 Apr 17; 348(16): 1537-45), Lakovou et al (JAMA. 2005 May 4; 293 (17): 2126-30), Stone et al (Circulation. 2009 Feb 24; 119(5): 680-6) and Marzocchi et al (Circulation. 2007 Jun 26; 115(25): 3181-8) - which were mainly observational studies and although ticlopidine was one of the drugs included in protocols, the results of the studies did not distinguish outcomes based on the particular thienopyridine used.
- 7.5 The Committee noted a meta-analysis of studies (Casella et al. Ital Heart J. 2003 Oct; 4(10): 677-84) comparing the clinical efficacy of clopidogrel and aspirin versus ticlopidine and aspirin after coronary stenting with bare metal stents. It involved 11,688 patients and at 30 days, the odds ratio (OR) for death and non-fatal MI was 0.63 in favour of clopidogrel and aspirin ($p=0.003$). OR for major adverse side-effects was 0.53 in favour of clopidogrel ($p<0.00001$). The Committee noted that safety data in the meta-analysis was limited to 7165 patients and showed that clopidogrel was also associated with non-significant trends of less neutropenia and thrombocytopenia (0.1% versus 0.22%, $p=0.3$) but a higher rate of major bleeding (2.4% versus 1.9%, $p=0.5$).
- 7.6 The Committee noted that the occurrence of serious haematological side-effects with ticlopidine has resulted in clopidogrel being used first-line in therapy. The side-effects include agranulocytosis, aplastic anaemia, neutropenia, pancytopenia, thrombocytopenia and thrombotic thrombocytopenic purpura (TTP). The Committee noted that the most commonly occurring case reports are for agranulocytosis and TTP but the most commonly occurring haematological side-effect in clinical trials is neutropenia. In a retrospective cohort study (Fukushima et al. Circ 2007; 71: 617-619), neutropenia

occurred at a rate of 0.7% with ticlopidine therapy. The Committee noted the TTP incidence rate of 0.02% in a cohort study involving 43,322 patients (Steinhubl et al. JAMA 1999; 281: 806-810) which occurred within the first eight weeks of treatment. Mortality rates with TTP were high (21%) although there were no deaths in those who received plasmapheresis. A systematic review of pharmacovigilance case reports established causality for agranulocytosis with ticlopidine (Level 2 evidence) and clopidogrel (Level 1 evidence) (Andersohn et al. Ann Intern Med. 2007; 146: 657-665). The Committee noted that in the TRITON-TIMI study (Wiviott et al. N Engl J Med 2007; 357: 2001-15), prasugrel carried a higher rate of major bleeding than clopidogrel (2.4% versus 1.8%, $p < 0.03$) but the rates of neutropenia with prasugrel were lower than for clopidogrel ($< 0.1\%$ versus 0.2% , $p = 0.02$). The Committee however noted that there is an indication of cancer risk (colonic neoplasms) with prasugrel (0.2% versus 0.1% , $p = 0.03$) (Wiviott et al. N Engl J Med 2007; 357: 2001-15) which is currently being investigated.

- 7.7 The Committee considered that the quality of evidence for ticlopidine use in DES is poor and the strength of evidence is weak. Although the available evidence shows that the rates of stent thromboses with ticlopidine do not appear to be substantially higher than those for the newer agents, the study designs and populations are not comparable. The Committee also noted that there was potentially cross-reactivity of ticlopidine in patients who were allergic to clopidogrel (Lokhandalawala et al. Circ Cardiovasc Interv. 2009 Aug; 2(4): 348-51). Ticlopidine is also associated with serious haematological side-effects. The Committee considered that although there is evidence for prasugrel in DES, the data on its rare but harmful side-effects like malignancies is less apparent as it is a newer agent. Based on the data available, the Committee considered that both ticlopidine and prasugrel would be appropriate in patients undergoing PCI who were clopidogrel-allergic.

Prasugrel in stent thrombosis

- 7.8 The Committee noted that the occurrence of stent thrombosis is not always due to failure of antiplatelet therapy but is also influenced by various factors for example location of lesion and stent mechanical factors. The Committee considered that there is currently no evidence for the use of prasugrel in the second-line setting after patients developed stent thrombosis whilst on clopidogrel and any effect of switching to prasugrel is only theoretical.
- 7.9 The Committee considered that clopidogrel should be considered the appropriate comparator to prasugrel in the second-line setting following stent thrombosis. The Committee noted that currently, the only evidence available for prasugrel in the second-line setting is indirect evidence from the TRITON-TIMI study (Wiviott et al. Lancet 2008; 371: 1353-63). The Committee considered that some of the aspects of the trial design, for example the lower loading dose of clopidogrel used, may have resulted in the efficacy difference between prasugrel and clopidogrel being overstated and this should be taken into account in the cost-utility analysis for prasugrel in this setting.
- 7.10 The Committee noted that the TRITON-TIMI study (Wiviott et al. Lancet 2008; 371: 1353-63) reported a stent thrombosis rate of 1.13% with prasugrel and 2.35% with clopidogrel ($p < 0.0001$) with an overall mortality rate from stent thrombosis of 22%. A Spanish registry study (de la Torre Hernandez et al. JACC Cardiovasc Interv. 2010 Sep; 3(9): 911-9) showed a recurrent thrombosis rate of 4.6% at 12 months in DES patients but the mortality rate was not reported.

- 7.11 The Committee considered the most appropriate data to model the mortality and MI rate would be from the Dutch registry study (van Werkum et al. *Circulation*. 2009 Feb 17; 119(6): 828-34) involving 431 patients. The rate of definite or probable recurrent stent thrombosis was 20.1%. The median follow-up time for this study was 27 months with 69% of the patients on clopidogrel and 87% of patients on aspirin at the time of the initial stent-thrombosis. The Committee noted that the myocardial infarction rate was 21%, the cardiac mortality rate was 12.3% and all-cause mortality rate was 15.4% at the end of the follow-up period.
- 7.12 The Committee noted that there was no head to head comparison of second line prasugrel compared to clopidogrel following a stent thrombosis event. Therefore the Committee considered it difficult to determine relative effectiveness of prasugrel over clopidogrel. The Committee noted the relative risk reduction estimated by PHARMAC staff from the TRITON-TIMI study (0.48) from the stent thrombosis rates for prasugrel and clopidogrel respectively was likely to be an overestimate of the treatments effectiveness. The Committee noted that prasugrel may indeed be no better than clopidogrel based on the lack of good quality evidence
- 7.13 The Committee noted that earlier studies indicated an association between the CYP2C19 and CYP2C9 genotype and reduced clinical efficacy of clopidogrel in terms of cardiac outcomes. A recent meta-analysis (Bauer et al. *BMJ*. 2011 Aug 4; 343: d4588. doi: 10.1136/bmj.D4588) showed that these genotypes do not predict coronary event rates. The Committee also considered that to date, there is no randomised controlled trial evidence that altering treatments on the basis of testing for either functional or genetic markers of lower responsiveness to thienopyridines alters clinical outcomes in any situation or after stent thrombosis.
- 7.14 The Committee considered that the definition of clopidogrel-allergy should be defined as: a history of anaphylaxis, urticaria or asthma within four hours of ingesting clopidogrel in non-asthmatic patients. The Committee also considered that the Special Authority criteria for prasugrel use following stent thrombosis whilst on clopidogrel should take into account patient compliance with clopidogrel prior to stent thrombosis event.

8 Sole Supply and Widening of Funded Access to Filgrastim

Application

- 8.1 The Committee reviewed an Application from PHARMAC staff for the listing of filgrastim in Section B of the Pharmaceutical Schedule for the management of neutropenia. The Committee also reviewed information relating to a Request for Proposals issued by PHARMAC for Hospital Supply Status and possibly Community Sole Subsidised Supply of filgrastim.

Recommendation

- 8.2 The Committee **recommended** that filgrastim should be listed in the Blood and Blood Forming Therapeutic Group of Section B of the Pharmaceutical Schedule subject to Special Authority criteria for the following patient groups:
- Prevention of neutropenia in patients undergoing high risk chemotherapy for cancer (Febrile Neutropenia risk \geq 20%); and

- For peripheral stem cell mobilisation in patients undergoing haematological transplantation; and
- Treatment of severe chronic neutropenia ($ANC < 0.5 \times 10^9/L$).

8.3 The Committee gave this **recommendation** a high priority. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee for specific advice regarding Special Authority criteria wording.

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

Discussion

8.5 The Committee noted that filgrastim (Neupogen, recombinant granulocyte colony-stimulating factor 300 µg and 480 µg prefilled syringes and 300 µg vial) is currently listed in Part II and III (Discretionary Community Supply Pharmaceuticals (DCS)) of Section H of the Pharmaceutical Schedule. Members noted that DCS funding is currently restricted to indefinite supply for any appropriate indication for the management of patients with cancer. Members noted that currently filgrastim was funded from DHBs own budgets and anecdotal reports from clinicians indicate that it may currently be underutilised due to budgetary constraints.

8.6 The Committee noted that filgrastim increases neutrophil production from stem cells, multipotent progenitors and myeloid progenitors and it also improves neutrophil function. The Committee noted that filgrastim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients receiving cytotoxic chemotherapy for malignancy and patients undergoing myeloablative therapy followed by bone marrow transplantation. Members noted it is also indicated for the mobilisation of stem cells in peripheral harvest in patients undergoing autologous or allogeneic stem cell transplantation, for long term use in patients with Severe Chronic Neutropenia (SCN) and treatment of persistent neutropenia in patients with advanced HIV infection.

8.7 The Committee considered that the best evidence for the use of filgrastim was in the prevention of febrile neutropenia in patients receiving cytotoxic chemotherapy for malignancy. Members reviewed evidence from a number of studies of filgrastim in this setting and the European Organisation for Research and Treatment of Cancer (EORTC) guidelines for prophylactic use of GCSFs to reduce the risk of chemotherapy-induced neutropenia (European Journal of Cancer 2011;47:8-32). Members noted that the EORTC guidelines recommended that GCSF prophylaxis should be used in patients undergoing chemotherapy where the risk of febrile neutropenia exceeded 20% or where the risk was between 10 to 20% with additional risk factors (e.g. age over 65 years, prior febrile neutropenia or advanced disease). Members noted that filgrastim resulted in an absolute risk reduction for febrile neutropenia of between 10% and 17%, with a number-needed-to-treat of between 6 -10. Members considered that filgrastim reduces the need for antibiotics and hospitalisation as well as possibly reduced mortality in this setting.

- 8.8 The Committee noted that filgrastim permits use of more intensive (dose-dense) chemotherapy regimens. However, members considered that whilst there is some evidence that more intensive chemotherapy regimens are associated with better survival, there is mixed evidence that overall survival or progression free survival is improved by the use of GCSFs.
- 8.9 The Committee considered that SCN was a set of uncommon disorders (around 10 per million population) that may be idiopathic, have a genetic basis or be associated with other disorders such as immune disorders (e.g. systemic lupus erythematosus) or glycogen storage disorders. Members noted that a number of applications for filgrastim for patients with SCN had been approved through the exceptional circumstances scheme. Members noted that the evidence for the use of GCSF in SCN was limited but considered that it was likely to reduce risk of infection, hospitalisations and mortality in this setting.
- 8.10 The Committee considered that the risks of short term administration of GCSF were musculoskeletal pain, excess white cells and platelets and headache in approximately 20% of patients. However, the risks of long term use were unclear. Members noted that one report indicated that about 20% of patients with chronic SCN developed myelodysplasia or acute leukaemia after 10 years; however, members considered that it was unclear if this was related to GCSF use or the underlying disease condition.
- 8.11 The Committee noted that there was no specific evidence available about the prevalence and severity of neutropenia (chemotherapy induced or SCN) in Maori and Pacific people, however members noted that these groups generally have a higher prevalence of cancers. Members further noted that older patients were at greater risk of chemotherapy-induced febrile neutropenia and children have a higher prevalence of SCN conditions.
- 8.12 The Committee considered that the current DCS funding criteria were quite flexible but did exclude some patients who would likely benefit from treatment. Members considered that if, as anecdotal reports suggested, filgrastim was currently being underutilised, funding in the community may result in cost savings through lower occurrence of febrile neutropenia, lower incidence of infections and reduced need for, and duration of, antibiotics and hospitalisation.
- 8.13 The Committee noted that PHARMAC had recently issued a Request for Proposals for Hospital Supply Status and possibly Community Sole Subsidised Supply of filgrastim. Members noted although full evaluation of the bids had yet to be completed, provisionally PHARMAC staff had selected a preferred bid from a generic supplier for a biosimilar brand of filgrastim. The Committee considered that in general, subject to Medsafe approval, there was no reason not to award sole supply status to biosimilar brands of biologic molecules and/or to reference price different brands of biologics.
- 8.14 The Committee reviewed the pack and presentations of the provisional best bid. Members noted that both the biosimilar and Neupogen (the incumbent brand) were available as 300 µg and 480 µg prefilled syringe presentations. However, members noted that the biosimilar brand was not available in a vial presentation. Members considered that although usage of the vial presentation was limited, it was an important presentation mainly in paediatrics. Members considered that the vial presentation enabled smaller doses to be prepared and vial sharing between paediatric patients was currently being used by DHBs to reduce wastage. Members considered that although the

prefilled syringes could be used for paediatrics, it would be difficult to deliver precise dosing.

9 Cevimeline for dry mouth (including Sjogren's syndrome)

Application

- 9.1 The Committee reviewed an application from [withheld under s 9(2)(a) of the OIA] for funding of cevimeline for the treatment of dry mouth (xerostomia) associated with Sjögren's syndrome.

Recommendation

- 9.2 The Committee **recommended** that cevimeline is funded for patients with the dry mouth symptoms of diagnosed Sjogrens syndrome where patients have trialed and are intolerant to pilocarpine with a low priority.
- 9.3 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.*

Discussion

- 9.4 The Committee considered that current treatment for Sjögren's syndrome (SS) centres around the management of dry mouth and eye symptoms using saliva substitutes, chewing gum, water or pilocarpine oral solution prepared from pilocarpine eye drops.
- 9.5 The Committee considered that there are no recognised clinical differences in the ocular or oral manifestations that would differentiate primary from secondary SS and the histopathologic changes are identical. The Committee noted that there are no head to head trials comparing pilocarpine and cevimeline so the evidence for the two treatments has been appraised separately.
- 9.6 Four studies of oral pilocarpine in SS have been identified. The Committee considered a 12-week multicentre double-blind study of 256 patients with SS (Papas et al. J Clin Rheumatol 2004; 10: 169-177). Patients either received pilocarpine 20mg for six weeks increasing to 30mg daily for a further six weeks or placebo. The pilocarpine group showed significant improvement in the global assessment of dry mouth symptoms in comparison to placebo and an increased dose response effect was observed. Salivary flow response rates were 46% at the 20mg dose and 61% at the 30mg dose. The authors reported that there was no improvement in dry eye symptoms during the 20mg dose phase of pilocarpine but patients reported a significant improvement when the 30mg daily dose was used. The Committee noted that 13% of the treatment group withdrew from the study although only 4% of these were reported to be caused by adverse events.
- 9.7 The Committee considered a 12-week multicentre double-blinded trial which studied the effect of 10 mg or 20 mg pilocarpine compared with placebo on 373 participants with SS (Vivino et al. Arch Intern Med 1999; 159: 174-181). No significant difference was reported between the 10mg pilocarpine and placebo group for either subjective

measures of dry eye or dry mouth symptoms. The authors reported that 20mg pilocarpine produced a significant improvement in oral symptoms in 61.3% of participants (31.1% for placebo) and ocular symptoms (42% compared with 26.1% for placebo).

- 9.8 The Committee considered a small 12-week double-blind study of 20 mg pilocarpine compared with placebo in 44 Taiwanese patients with SS (Wu et al. J Formos Med Assoc 2006; 105 (10): 796-803). The authors reported that 69.6% of participants had improvement in the sensation of dry mouth as assessed by a participant completed visual analog scale compared to 23.8% in the placebo group.
- 9.9 The Committee considered a randomised non-blinded 12-week study (Tsifetaki et al. Ann Rheum Dis 2003; 62: 1204-1207) which compared the effects of either 10mg per day pilocarpine, artificial tears or inferior puncta occlusion on the symptoms of SS. The Committee noted that pilocarpine appeared to have a beneficial effect in 90% of participants according to a subjective visual analogue scale which was a significantly higher response than to the alternative treatments. The Committee noted that there were no withdrawals from this group and also noted that the results contrast to other studies showing a minimal to no ocular response to lower dose oral pilocarpine.
- 9.10 The Committee considered that overall, the four studies suggest that 46% to 70% of patients will have some improvement in dry mouth symptoms with a 20 to 30 mg per day total dose of oral pilocarpine. The Committee considered that oral pilocarpine may result in a modest improvement in symptoms of dry eye although evidence for this is less clear. The Committee considered that oral pilocarpine is reasonably well tolerated with the major adverse effects being sweating, urinary frequency, flushing and excess salivation.
- 9.11 The Committee considered four studies assessing the safety and efficacy of cevimeline. The Committee considered a double-blinded study of 75 SS patients randomised to receive 30mg or 60mg of cevimeline taken three times daily or placebo for six weeks (Fife et al. Arch Intern Med 2002; 162: 1293-1300). The primary endpoint was a subjective patient assessment of 'better' 'no change' or 'worse' and additionally, a visual analog scale assessment for six measures of dry mouth including dryness of tongue and ability to speak. There was also an objective measure of pre and post-dose saliva production. The Committee considered that overall more patients in the active treatment group reported their symptoms as 'better', with the 30mg dose appearing more effective (72%-30mg, 30%-placebo, 52%-60mg). The Committee noted that cevimeline significantly increased measured saliva flow but had no effect on objective measure of lacrimal flow. The Committee noted that adverse events (sweating, nausea, headache, rigors and diarrhoea, dyspepsia and dizziness) appeared to be somewhat dose-related with all subjects in the 60mg group reporting an adverse event and 33% of them withdrawing due to these while 88% of the 30mg group suffered at least one adverse event, with 27% withdrawing for this reason.
- 9.12 The Committee noted the results of a randomised double-blinded crossover study of 50 southern Chinese SS patients who received cevimeline 30mg or placebo three times daily for 10 weeks followed by a four week washout and treatment cross-over (Leung et al. Clin Rheumatol 2008; 27: 429-436). Reported outcomes were changes in patient reported oral and ocular symptoms assessed using validated questionnaires and also a stimulated saliva flow measurement. The Committee considered that the study showed a positive trend toward improvement with active treatment; however, there was no

statistically significant difference in outcomes between the placebo and cevimeline treatment phases.

- 9.13 The Committee considered a study involving 60 patients with suspected or diagnosed SS randomised to receive 20 mg or 30mg of cevimeline or placebo three times daily for four weeks which showed little effect on symptoms of dry eye (Ono et al. *Am J Ophthalmol* 2004; 138: 6-17). The Committee noted that the results reported some sporadic statistically significant results despite there appearing to be little difference amongst the groups and more than three quarters of both treatment arms classed the treatment as 'not useful'.
- 9.14 In a 12-week controlled trial in 197 patients with SS, patients received of 15 mg or 30 mg cevimeline or placebo three times daily (Petroni et al. *Arthritis and Rheumatism* 2002; 46 (3): 748-754). The primary efficacy end point was patient's global evaluation of dry eyes, dry mouth and overall dryness rated as 'better' 'worse' or 'no change'. Objective endpoints were measures of salivary and tear flow. The authors reported a statistically significant increase in patients global evaluation of dry mouth at study end point between the placebo group (37% 'better') and the 30mg treatment group (66% 'better') and that there was also improvement in dry eye symptoms, with 39% 'better' for cevimeline and 24% for the placebo group. Overall dryness was reported as better in 66% of 30 mg treatment patients compared with 36% of placebo group. The Committee considered that the results from the 15mg treatment group were similar to those in the placebo group. The Committee noted that there was a statistically significant increase in salivary flow between the placebo and 30mg treatment groups while lacrimal flow data was less convincing.
- 9.15 The Committee considered that the strength and quality of the evidence reviewed for cevimeline was weak. The evidence for cevimeline's effect on saliva flow is from two randomised placebo- controlled double-blind studies and a cross-over study with all studies having a small number of participants. The Committee considered that the studies appear to be reasonably well designed but are compromised by incomplete and/or selective reporting of data, inadequate power and a high and variable placebo effect. The Committee considered that the results are not particularly convincing with an inconsistent response across the studies. Overall, the Committee considered that cevimeline appears to have a moderate effect on salivary flow but with many patients suffering adverse side effects.
- 9.16 Using an indirect comparison of outcomes from pilocarpine and cevimeline studies, the Committee considered that the pooled absolute risk difference between treatments is similar and therefore the two treatments are likely to be equally effective.
- 9.17 The Committee considered that cevimeline treatment appears to have a positive effect on dry mouth, but there appears to be less effect on dry eye symptoms. The Committee considered that due to the higher cost of treatment and less convincing evidence it may be useful as a second line treatment for those patients who are intolerant to pilocarpine. The Committee considered that around 30 to 50% of patients could have limited response to pilocarpine and that these patients may respond to cevimeline however, evidence to support the efficacy of cevimeline in those who do not respond to pilocarpine has not been found. The Committee noted that it may be useful to find a supplier for pilocarpine tablets which may be better tolerated than the pilocarpine oral solution currently being used.

- 9.18 The Committee considered that the dry mouth symptoms of SS have a major impact on eating, speech, sleep and oral hygiene. The Committee considered that patients who respond to treatment are likely to experience improved oral health with increased saliva flow but there is no evidence of a reduction in oral candidiasis

10 Valganciclovir for stem cell transplant

Application

- 10.1 The Committee reviewed an application from the Haematology Society of New Zealand for the listing of valganciclovir on the Pharmaceutical Schedule for prophylaxis of cytomegalovirus (CMV) in haematopoietic stem cell transplant (HSCT) patients.

Recommendation

- 10.2 The Committee **recommended** that valganciclovir be listed on the Pharmaceutical Schedule under Special Authority for pre-emptive therapy for CMV following HSCT with a high priority.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 10.3 The Committee considered that CMV caused pneumonia, gastroenteritis and less commonly retinitis and hepatitis in HSCT recipients. Members noted that CMV pneumonia in the HSCT setting had a mortality rate of between 15 and 80%.
- 10.4 The Committee noted that the serostatus of the recipient was a more important risk factor for CMV disease than the serostatus of the donor. Members considered it was important that CMV seronegative patients should not receive donations from CMV seropositive donors.
- 10.5 The Committee noted that CMV prophylactic therapy was no longer recommended due to a lack of survival benefit. Members considered that pre-emptive therapy against CMV was now the standard of care. The Committee noted that pre-emptive therapy for CMV relies on detection of primary or reactivated CMV infection by quantitative real-time polymerase chain reaction (PCR) or antigen testing and initiation of antiviral treatment.
- 10.6 The committee reviewed the Boeckh et al study (Blood 1996; 88: 4063-71) comparing prophylactic versus pre-emptive therapy for CMV following HSCT. Members noted that this randomised study of 184 patients comparing valganciclovir prophylaxis or placebo until day 270 or valganciclovir (twice daily) if CMV DNA was >1,000 copies/ml. The Committee noted that there was no difference between the groups at the primary endpoint (a composite of CMV disease or invasive bacterial/fungal infection or death by

day 270). Members noted that the study showed no difference in mortality between prophylactic versus pre-emptive valganciclovir therapy post HSCT.

- 10.7 The Committee noted that since the Boeckh et al study assays for CMV had become more sensitive and refinements had been undertaken in pre-emptive treatment strategy.
- 10.8 The Committee considered that intravenous (IV) ganciclovir was 'Standard of Care' for pre-emptive therapy of CMV. The Committee noted the van der Heiden et al study (Bone Marrow Transplantation 2006; 37: 693-698) a non-randomised observational study examined the efficacy and safety of oral valganciclovir or IV ganciclovir in pre-emptive treatment of CMV in T-cell depleted allogeneic stem cell transplant recipients. Members noted that pre-emptive treatment with either valganciclovir or IV ganciclovir lead to a similar reduction of CMV DNA load.
- 10.9 The Committee considered the Winston et al study (American Society for Blood and Marrow Transplantation 2006; 12:635-640) an open label cross over study investigating the pharmacokinetics of ganciclovir following IV ganciclovir and oral valganciclovir. The plasma ganciclovir concentration following oral valganciclovir was found to be non-inferior to IV ganciclovir.
- 10.10 The Committee considered that oral valganciclovir had comparable efficacy to IV ganciclovir. Members noted that valganciclovir was an oral therapy and thus would reduce the need for IV access and hospitalisations would be minimised, particularly as IV ganciclovir was often used as a twice a day regimen.
- 10.11 The Committee noted the paper by Mori and Kato (Int J Hematol 2010; 91:588-95). Members considered that risk adaptive approach to pre-emptive therapy should be used based on the comment that 'a lower threshold should be used for high risk patients, and a higher threshold should be used for low risk patients'. Members considered that this approach could reduce the patients who receive antiviral agents without increasing the incidence of CMV disease, but that this would be difficult to include in a Special Authority
- 10.12 The Committee **recommended** that PHARMAC staff seek the advice of the Anti-Infective Subcommittee with respect to renewal criteria for pre-emptive therapy for CMV following HSCT. The Committee considered that the following restriction would be appropriate for valganciclovir for HSCT pre-emptive therapy

Patient is an allogeneic stem cell transplant recipient with evidence of either

(a) CMV reactivation

- DNA or antigen based testing,
- Dose 900mg BD x 2 weeks followed by 900mg daily up to 4 weeks depending on achievement of PCR / antigen negativity on 2 occasions a week apart, OR

(b) CMV infection

- documented CMV colitis / pneumonitis / other infection
- for use in maintenance phase following IV Ganciclovir based induction therapy
- duration of up to 6 weeks depending on clinical response.

11 Valganciclovir for solid organ transplant cytomegalovirus prophylaxis

Application

- 11.1 The Committee reviewed a PHARMAC staff proposal for the listing of valganciclovir on the Pharmaceutical Schedule for prophylaxis of cytomegalovirus (CMV) in solid organ transplant patients.

Recommendation

- 11.2 The Committee **recommended** that valganciclovir be listed on the Pharmaceutical Schedule under Special Authority for prophylaxis of CMV following solid organ transplant with a high priority.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 11.3 The Committee noted that valganciclovir is currently available for up to 14 weeks supply for cytomegalovirus (CMV) retinitis in immunocompromised patients and prophylaxis of CMV following solid organ transplant under Discretionary Community Supply (DCS). The Committee noted that there were approximately 174 solid organ transplants in New Zealand per annum and currently any requiring CMV prophylaxis could access this through the DCS.
- 11.4 The Committee noted that CMV infection is common after solid organ transplant, particularly in the first few months post transplant. Members noted that this was either due to CMV infection in the donor or blood products or a recurrence of a dormant CMV infection in the recipient due to immunosuppression. Members considered that CMV infection was unlikely if both donor and recipient were CMV negative and that this should be included in the decision for consideration of prophylaxis.
- 11.5 The Committee reviewed the Cochrane Review 2010 (Antiviral medication for preventing cytomegalovirus disease in solid organ transplant recipients) for CMV prophylaxis in solid organ transplant recipients. Members noted that those in the placebo and no treatment arms had a 30% chance of having CMV disease, 49% chance of CMV infection and a 2.3% chance of death by CMV. Members considered that death rates from CMV varied between the type of organ transplanted, with lung transplant patients having the highest death rate.

- 11.6 The Committee noted that the current therapies available in New Zealand included in the Cochrane review were aciclovir, valaciclovir and intra-venous (IV) ganciclovir. The Cochrane review comprised of 347 studies involving 3850 participants on these agents or placebo/no treatment and found that as a group antivirals reduced the risk of CMV disease by 60%, reduced all cause mortality by 40% (predominantly by CMV mortality reduction) as well as reducing herpes infections by 70%, bacterial infection by 35% and protozoal infections by 70%. These reductions were independent of the type of organ or duration of therapy compared to placebo/no treatment.
- 11.7 The Committee noted that the only direct comparator study in the review between oral valganciclovir and iv ganciclovir found no significant difference in CMV infection, CMV syndrome, CMV disease, all cause mortality or adverse events between the two products. Members noted that kidney transplant patients did better on valganciclovir than iv ganciclovir.
- 11.8 The Committee noted the Palmer et al study (Ann Intern Med 2010; 152:761-769) comparing extended valganciclovir against placebo in lung transplant patients. This randomised double blind study enrolled 136 patients on either three months valganciclovir and nine months placebo or 12 months valganciclovir. 4% of patients on 12 months valganciclovir had CMV disease compared with 32 % of patients on the three month course at 300 days post transplant. Members noted that in lung transplant patients on 12 months valganciclovir had significantly reduced CMV infection, disease and disease severity without increased ganciclovir resistance or toxicity
- 11.9 The Committee considered that valganciclovir would be preferred as it was a once or twice daily oral therapy compared to iv ganciclovir or valaciclovir orally four times a day. Members noted that aciclovir was indicated for this condition however this required one month of iv therapy followed by six months of oral therapy at 800mg four times a day.
- 11.10 The Committee noted the tabled Auckland District Health Board protocols regarding CMV prophylaxis following transplant. The Committee recommended that PHARMAC staff seek the advice of the Anti-Infective Subcommittee with respect to the Special Authority criteria for valganciclovir therapy following solid organ transplant. The Committee considered that the following restriction would be appropriate for valganciclovir for solid organ transplant:

Prophylaxis

Adult renal, liver and cardiac transplant CMV prophylaxis

Approvals valid for 90 days for applications meeting the following criteria:

- 1) Patient has undergone a kidney, liver or heart transplant
- 2) Donor CMV positive and recipient CMV negative

Adult renal, liver and cardiac transplant CMV

Approvals valid for 21 days for applications meeting the following criteria:

- 1) Patient has undergone a kidney, liver or heart transplant
- 2) Patient meets any of the following CMV serostatus
 - i. Donor CMV positive and recipient CMV negative, or
 - ii. Donor CMV negative and recipient CMV positive, or
 - iii. Donor CMV positive and recipient CMV positive

Lung transplant CMV prophylaxis

Approvals valid for 12 months for applications meeting the following criteria:

- 1) Patient has undergone a lung transplant
- 2) Patient meets any of the following CMV serostatus
 - i. Donor CMV positive and recipient CMV negative, or
 - ii. Donor CMV negative and recipient CMV positive, or
 - iii. Donor CMV positive and recipient CMV positive

Paediatric renal transplant CMV prophylaxis

Approvals valid for 90 days for applications meeting the following criteria:

- 1) Paediatric patient has undergone a kidney transplant
- 2) Paediatric patient meets any of the following CMV serostatus
 - i. Donor CMV positive and recipient CMV negative, or
 - ii. Donor CMV negative and recipient CMV positive, or
 - iii. Donor CMV positive and recipient CMV positive

Paediatric liver transplant CMV prophylaxis

Approvals valid for 90 days for applications meeting the following criteria:

- 1) Paediatric patient has undergone a liver transplant
- 2) Paediatric patient meets any of the following conditions
 - i. Donor CMV positive and recipient CMV negative, or
 - ii. Transplant for acute liver failure, or
 - iii. Re-transplantation, or
 - iv. Patient receiving OKT3

Consolidation course following CMV treatment

Approvals valid for 30 days for applications meeting the following criteria:

- 1) Patient has undergone a transplant, and
- 2) Patient has received iv ganciclovir for treatment of CMV disease