PTAC meeting held 8 & 9 May 2008

(minutes for web publishing)

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> ""**Minute"** means that part of the record of a PTAC or Sub-committee meeting (including meetings by teleconference and recommendations made by other means of communication) that contains a recommendation to accept or decline an application for a new investment or a clinical proposal to widen access and related discussion."

Note that this document is not necessarily a complete record of the PTAC meeting; records relating to PTAC discussions about an application that do not contain a recommendation to accept or decline an application have not been published and some material has been withheld in accordance with the following withholding grounds in the Official Information Act 1982 (OIA) to:

- protect the privacy of natural persons (section 9(2)(a);
- 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));
- enable PHARMAC to carry on, without prejudice or disadvantage, negotiations, including commercial negotiations (section 9(2)(j)).

Contents

1 Record of PTAC meeting held 21 & 22 February 2008

1.1 The Committee reviewed the record of the PTAC meeting held on 21 & 22 February 2008 and made the following minor amendments:

1.1.1 Sorafenib (Nexavar) – paragraph 8.3: replace "the very high cost of sunitinib was not justified for an essentially a palliative treatment" with "the very high cost of sunitinib was not justified for an essentially palliative treatment".

1.1.2 Sorafenib (Nexavar) – paragraph 8.7: replace "deaths were reported in 154 (34%) of patients" with "deaths were reported in 154 (34%) patients".

1.1.3 Ciprofloxacin/Hydrocortisone (Ciproxin HC) – paragraph 20.3: replace "applicants suggest ciprofloxacin with hydrocortisone ear drops are non-ototoxic" with "applicants suggest that ciprofloxacin with hydrocortisone ear drops are non-ototoxic".

1.1.4 Ciprofloxacin/Hydrocortisone (Ciproxin HC) - paragraph 20.13: replace "ciprofloxacin with hydrocortisone ear drop were a safer alternative to use" with "ciprofloxacin with hydrocortisone ear drops were a safer alternative to use".

1.1.5 Multivitamin for children on ketogenic diet – paragraph 24.6: replace "dietary protocol from Johns Hopkins wasn't provided with application" with "dietary protocol from Johns Hopkins wasn't provided with the application"

2 Antiretrovirals for Post Exposure Prophylaxis following non-occupational exposure to HIV

2.1 The Committee reviewed the Anti-infective Subcommittee of PTAC's minutes and recommendations regarding an application for funding antiretrovirals for non-occupational Post Exposure Prophylaxis to HIV infection (nPEP).

2.2 The Committee noted that the Subcommittee had assessed an application from the AIDS Medical and Technical Advisory Committee (AMTAC) for the funding of antiretrovirals for prophylaxis of HIV infection following non-occupational exposure. The Committee noted that the application was for standard triple antiretroviral therapy for 28 days, commencing within 72 hours of exposure; exposure being to individuals confirmed to have HIV.

2.3 The Committee noted that the Subcommittee's recommendation was for funding to be restricted to patients considered to have had a high risk exposure (risk of transmission >1 in 300), notably patients who have had receptive anal intercourse or shared intravenous injecting equipment with individuals known to be HIV-positive.

2.4 The Committee noted the Subcommittee's assessment of the evidence. Evidence for using antiretrovirals for nPEP was based on animal studies; occupational exposure prophylaxis practices; perinatal practices to reduce vertical transmission; observational studies and case reports; and there was a lack of data from randomised controlled trials, considered to be difficult to obtain due to ethical issues with randomised clinical trials of nPEP. Additional support for the practice of using antiretrovirals for nPEP came from the Australian National Guidelines for n-PEP (2007) and the United States Department of Health and Human Services (CDC) guidelines (2005), both of which recommend antiretroviral use for n-PEP depending on the degree of risk and from a literature review by the Australasian Society of HIV Medicine Inc (*ASHM Journal Club, 2006*).

2.5 The Committee noted that, in an observational study by Poynten et al *(Poynten et al 2007, HIV Medicine)*, a low number of seroconversions (3 seroconversions) were noted after treatment completion with most of the reported cases having evidence of ongoing high risk behaviour. The Committee also noted that cases of n-PEP treatment failure have been described in the literature, with studies reporting non-completion of treatment due to high levels of adverse effects.

2.6 The Committee noted that PHARMAC staff had reviewed a published analysis by Pinkerton et al *(Pinkerton et al 2004, AIDS*), which calculated the cost-effectiveness of nPEP from a societal perspective in the US. The Committee noted that PHARMAC staff consider the cost per QALY of nPEP is likely to be high and uncertain because of the dependence on assumptions including the risk of transmission with exposure, the cost of prophylaxis and its effectiveness in reducing the rate of transmission. The Committee considered that PHARMAC staff should undertake a cost-utility analysis to determine the cost-effectiveness of nPEP in New Zealand.

2.7 The Committee noted the Subcommittee's concern that a potential risk of funding antiretrovirals for nPEP could be a decrease in risk-reduction behaviours. The Committee noted that in the Poynton et al study, 14% of patients had a previous nPEP treatment and despite the apparent success of nPEP programmes, the incidence of newly acquired HIV infections over the study duration was 1138 with an estimated number of new infections prevented being between one and nine during the study period.

2.8 The Committee agreed with the Subcommittee's view that the most effective, and cost-effective methods for preventing HIV infection were risk reduction behaviours that protect against exposure to HIV and that antiretrovirals cannot replace these behavioural approaches. The Committee considered that emphasis should be placed on educational and behavioural approaches to preventing HIV exposure and that nPEP would be unlikely to reduce the prevalence of HIV infections significantly. However, the Committee considered that the use of antiretrovirals to prevent HIV infection after non-occupational exposure was appropriate in high-risk situations such as receptive anal intercourse or sharing of intravenous injecting devices with individuals known to be HIV positive.

2.9 The Committee confirmed that the threshold of transmission risk of 1 in 300 or higher, as recommended by the Subcommittee, was the appropriate level at which antiretroviral therapy for nPEP should be considered.

2.10 The Committee considered that it could not estimate the number of people who would access antiretrovirals for nPEP. However, the Committee considered that other factors

such as the prevalence of HIV infection in New Zealand would influence the total cost of using antiretrovirals for nPEP.

2.11 The Committee **recommended** that access to antiretrovirals be widened to include a 28-day treatment course of a combination of up to 3 antiretrovirals, initiated within 72 hours post exposure, for the following patient groups:

- patients who have had receptive anal intercourse with a known HIV positive person, or
- patients who have had shared intravenous injecting equipment with a known HIV positive person.

2.12 The Committee gave this recommendation a high priority.

2.13 The Committee also considered that the mechanisms for accessing antiretroviral therapy for nPEP should be the same as the current mechanism for accessing treatment of HIV; that is, through Special Authority application from a named specialist who could determine the appropriate nPEP regimen on a case-by-case basis. The Committee noted that patients could be started using 3-day hospital "starter packs" while Special Authority applications were processed. The Committee further considered that mechanisms would need to be put in place to allow access to packs during periods such as public holidays.

2.14 The Decision Criteria 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

3 Ketotifen fumarate (Zaditen) for ocular allergy

3.1 The Committee reviewed an application from Novartis for the funding of ketotifen fumarate (Zaditen) 0.025% eye drops for the treatment of seasonal allergic conjunctivitis (SAC). The Committee noted that the application was for both the multidose pack (5 mL) and the preservative-free single-dose units (20 x 0.4 mL).

3.2 The Committee noted that ketotifen is a benzocycloheptathiophene derivative that inhibits the release of chemical mediators from mast cells, which occurs in type 1 allergic reactions. Ketotifen also inhibits the attraction and migration of eosinophils and is a potent histamine-1 (H_1) receptor antagonist with a relatively high affinity for the H_1 receptor.

3.3 The Committee noted that this new topical form of ketotifen with low systemic absorption was indicated for the treatment of seasonal allergic conjunctivitis, an ocular allergic condition that affects a large number of patients seen in primary care. The Committee also noted that an oral liquid form of ketotifen is currently funded.

3.4 The Committee noted that the evidence of efficacy for ketotifen fumarate 0.025% eye drops was from clinical phase III studies, the majority of which were published in 2003. The Committee also noted that the eye drops were registered in New Zealand in 2004 and that, from the information contained in the product datasheet for ketotifen fumarate eye drops, there were no major safety concerns. The Committee noted that the product was licensed for use in patients aged three and over.

3.5 The Committee noted that there were several eye drop preparations available for the treatment of SAC, both in the over-the-counter and prescription markets. The Committee noted that eye drops currently funded for ocular allergy included the partly subsidised antihistamine, levocabastine eye drops, and fully subsidised mast cell stabilisers, lodoxamide and sodium cromoglycate eye drops. The Committee noted that there are some fully funded ocular decongestants and ocular lubricants available that are sometimes used for the management of SAC.

3.6 The Committee evaluated the evidence for ketotifen fumarate from five studies; two studies (Study 1 and 2) assessed safety and efficacy and three studies (Study 3, 4 and 5) compared ketotifen to either placebo or active comparator eye drops. Study 1 and 2 were "conjunctival allergen challenge (CAC)" studies that demonstrated that ketotifen was superior to placebo in reducing itching and redness. Study 1 *(Abelson et al. 2003 Arch Ophthalmology)* reported efficacy at 15 minutes to 8 hours after allergen challenge. Study 2 (*Greiner et al. 2003 Am J Ophth)* reported that efficacy continued at 4 weeks with regular twice-daily treatment. Both studies reported a low incidence of side effects.

3.7 Study three *(Greiner and Minno 2003 Clin Therapeutics)* compared ketotifen to nedocromil and placebo using a CAC study model with a single dose of the active agent or the comparator instilled after allergen challenge. Results indicated that ketotifen-treated eyes experienced significantly less ocular itchiness than those treated with nedocromil or placebo. Comfort scores were greater for ketotifen than for nedocromil. The Committee considered that the nedocromil dose used in this study was lower than the recommended dose.

3.8 The Committee noted that Study 4 *(Crampton 2003 Clin Therapeutics)* was a randomised double-blind placebo and active comparator controlled trial that compared ketotifen eye drops alone to desloratadine tablets alone or in combination using a CAC model. The Committee noted that the data indicated greater efficacy for ketotifen eye drops than desloratadine tablets and superiority of the combination over drops alone for reducing redness. However, the Committee considered that the study had limited generalisability (experimental rather than real-life).

3.9 The Committee considered that Study 5 *(Kidd et al. 2003 Br J Ophth)* provided evidence that was relevant to the clinical setting. The Committee noted that Study 5 was a randomised double-blind environmental study that compared ketotifen eye drops to levocabastine eye drops and placebo for the treatment of SAC. The results indicated that for the primary outcome (subjective assessment of efficacy) there was no statistical difference between ketotifen and levocabastine, although there was a trend favouring ketotifen. For secondary outcome measures (symptom scores and symptom-free days), ketotifen was marginally superior to levocabastine for composite symptoms scores, but not significantly different for symptom-free days. Assessment of safety showed that there were two serious non-ocular adverse events reported in the ketotifen group and two serious ocular adverse events in the placebo group. The Committee considered that the

design of the study was adequate, although the wash-out period for non-study mast cell stabilisers prior to randomisation was short. The Committee noted that patients were allowed to use nasal sprays and asthma medication during the study.

3.10 The Committee considered that the evidence reviewed indicated that ketotifen eye drops were safe and effective for the treatment of SAC. The Committee noted that the data indicated that ketotifen eye drops had the same or similar therapeutic effect and safety as levocabastine eye drops and considered that they could be reference priced. The Committee **recommended** that the multidose presentation of ketotifen eye drops be listed on the Pharmaceutical Schedule only if it was cost-neutral compared to levocabastine eye drops. The Committee did not recommend listing the single dose vials.

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

4 Entecavir and pegylated interferon for hepatitis B

4.1 The Committee reviewed its previous recommendations for entecavir and pegylated interferon for the treatment of chronic hepatitis B, in light of the recommendations made by the Hepatitis B Ad Hoc Subcommittee of PTAC, and a subsequent cost-utility analysis provided by PHARMAC on the treatments for chronic hepatitis B.

4.2 The Committee noted that it had previously reviewed applications for the funding of entecavir and pegylated interferon for the treatment of chronic hepatitis B. The Committee noted that it had requested that the Hepatitis B Ad Hoc Subcommittee review the current treatment options for hepatitis B in New Zealand, including the potential and optimal use for entecavir. The Committee noted that the Subcommittee had recommended that entecavir be listed on the Pharmaceutical Schedule as first-line monotherapy for treatment-naïve patients, and that patients in whom treatment has failed, entecavir treatment should be switched to adefovir or have adefovir added to their entecavir treatment. Regarding pegylated interferon, the Committee also noted that the Subcommittee recommended that pegylated interferon be listed on the Pharmaceutical Schedule with medium priority for HBeAg negative patients without cirrhosis. The Committee noted that the Subcommittee had recommended that treatment of hepatitis B should commence in patients who are HBsAg positive and either HBeAg positive or have ≥ 20,000 HBV DNA IU per ml and have at least Metavir stage 2 fibrosis on liver histology.

4.3 The Committee noted that there were approximately 40,000 to 85,000 people with chronic hepatitis B in New Zealand and patients would be either HBeAg positive or HBeAg negative at the time of diagnosis and there would be equal numbers of each. The Committee noted that there are currently three fully funded treatments listed on the

Pharmaceutical Schedule for chronic hepatitis B; lamivudine, adefovir and standard interferon.

4.4 The Committee noted that evidence for lamivudine indicated that while there was an initial response in 70-90% of patients, sustained response was only seen in about 30-40% of patients by year three due to a progressive increase in viral resistance. The Committee noted that viral resistance occurred in up to 70% of patients by 4–5 years, and that because of high resistance, current international guidelines no longer recommended lamivudine as first-line treatment. However, the Committee noted that lamivudine remains the first choice of treatment in children with chronic hepatitis B, as it is the only registered treatment available for children.

4.5 The Committee noted that standard interferon was effective in 20-40% of patients with sustained response in 90% of the initial responders; however, acceptance of therapy was low (less than 5% of patients) because of poor tolerability, lack of efficacy and the intensive follow-up that was required.

4.6 The Committee noted that longer-term (out to four years) evidence for adefovir in treatment-naïve patients was now available and indicated that adefovir was effective in treatment-naïve HBeAg positive patients, with lower rates of resistance compared to lamivudine (up to 29% at five years). The Committee noted that adefovir is not registered for this indication although it is considered to be the treatment of choice for lamivudine and entecavir-resistant patients.

4.7 The Committee noted that it had previously reviewed the evidence for pegylated interferon in the treatment of chronic hepatitis B and considered that pegylated interferon had superior efficacy compared to standard interferon and lamivudine, with a seroconversion rate of 32% in HBeAg positive patients. The Committee noted that the Subcommittee considered that the adverse effects of pegylated interferon were comparable to those of standard interferon, but that the different dosing schedule for pegylated interferon may improve compliance. Furthermore, the Committee noted that the Subcommittee considered that, unlike other hepatitis B treatments, pegylated interferon had the potential to “cure” 4% of patients, but the high cost, inconvenience of administration and the need for close monitoring would mean that treatment should be reserved for patients who are likely to respond and comply with treatment. Ideal candidates would be young HBeAg positive patients.

4.8 The Committee noted that PHARMAC had reviewed and revised the supplier’s cost-utility analysis on pegylated interferon for hepatitis B. The Committee considered that the assumptions in the analysis were reasonable. However, the Committee noted that if entecavir was funded, patients would receive entecavir (rather than lamivudine) following relapse after treatment with pegylated interferon. The Committee considered that this should be incorporated into the analysis. The Committee noted that the evidence for entecavir indicated that it was superior to lamivudine in nucleoside-naïve HBeAg positive patients with significantly lower resistance rates at four years. Response rates for entecavir were also better than adefovir in treatment-naïve patients with lower rates of resistance with entecavir. The Committee noted that entecavir was considered safe with rates of adverse effects similar to those with adefovir. The Committee also noted that entecavir was not recommended for patients with chronic hepatitis B who were co-infected with HIV and receiving Highly Active Antiretroviral Therapy (HAART), due to the potential for increased HIV resistance. The Committee noted that while there is some

evidence to suggest that entecavir is effective in lamivudine-resistant HBeAg positive patients, entecavir is not recommended for treatment of lamivudine-resistant patients due to the risk of cross resistance (resistance rates approximately 42% at four years).

4.9 Furthermore, the Committee noted the recommendations of the American Association for the Study of Liver Diseases guidelines 2007 (AASLD) which recommend that, in treatment-naïve HBeAg positive and negative patients, treatment could be initiated with any agent although entecavir, adefovir or pegylated interferon were the preferred agents due to the high rates of lamivudine resistance. The Committee noted the AASLD recommendations for patients who developed resistance to treatment, and considered that treatment of such patients required additional consideration.

4.10 The Committee noted the proposed Special Authority criteria for entecavir for the treatment of chronic hepatitis B recommended by the Subcommittee, but considered that it would like to review the evidence for the criteria that were recommended.

4.11 The Committee also noted the recommendation from the Subcommittee regarding amendments to the Special Authority criteria for lamivudine as follows: To change the requirement for a viral load of greater than 100,000 HBV DNA copies per ml to a viral load greater than or equal to 20,000 HBV DNA IU per ml; and to have at least Metavir stage 2 fibrosis on liver histology (rather than ALT > 2 x ULN or Metavir stage 3 or 4).

4.12 The Committee noted that an estimated 600 treatment-naïve patients with chronic hepatitis B were referred to secondary care each year for antiviral therapy. The Committee considered that, of these, 40% would be HBeAg positive, 90% of whom would have confirmed HBeAg positive chronic disease and would meet the criteria for therapy. The remaining 60% would be HBeAg negative of whom only 40% would have confirmed HBeAg negative chronic disease, with the rest having low levels of HBV DNA and other causes of liver dysfunction; this latter group would not require antiviral therapy against HBV. Therefore approximately 360 treatment-naïve patients would start treatment for chronic hepatitis B each year, with approximately 310 remaining on treatment for at least two years. The Committee noted that of the estimated 360 patients requiring therapy, approximately 15% would be involved in new clinical trials leaving 85% who would seek funded treatment for chronic hepatitis B. It is estimated that, of these, approximately 15% would seek treatment with pegylated interferon while the remainder would opt for an oral antiviral agent. This equates to 240-250 patients opting for entecavir and 50-60 for pegylated interferon. The Committee noted a similar distribution of treatment options was seen in Australian data.

4.13 The Committee considered the cost-utility analysis provided by PHARMAC staff on entecavir for hepatitis B. The Committee considered that the analysis had overestimated the long-term resistance rate for entecavir. The Committee noted that current evidence indicates that rate of resistance at year four was 0.8%, and considered that this was unlikely to significantly increase over time.

4.14 After consideration of the evidence and cost-effectiveness information the Committee considered that both treatments were effective for the treatment of chronic hepatitis B and that each agent may be more suited to a different patient population than the other.

4.15 The Committee **recommended** that entecavir should be listed on the Pharmaceutical Schedule with high priority for the treatment of chronic hepatitis B in treatment-naïve patients.

4.16 The Committee considered that treatment of chronic hepatitis B with pegylated interferon would be appropriate in a smaller proportion of patients (approximately 10-20% of patients). Therefore, the Committee **recommended** that pegylated interferon be also listed on the Pharmaceutical Schedule with a high priority for the treatment of chronic hepatitis B in treatment-naïve patients.

4.17 The Committee considered that access to both entecavir and pegylated interferon should be through Special Authority application and that the criteria would be determined using the evidence available.

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

5 Zolmitriptan (Zomig) nasal spray and tablets for the treatment of migraine

5.1 The Committee considered an application from AstraZeneca for the listing of zolmitriptan 5 mg nasal spray and zolmitriptan 2.5 mg and 5 mg tablets on the Pharmaceutical Schedule for the acute treatment of migraine with or without aura.

5.2 The Committee noted that it had previously considered an application from AstraZeneca to list zolmitriptan 5 mg nasal spray and had recommended that the application be declined. The Committee noted that the supplier had provided information to try to address some of the Committee's previous concerns about zolmitriptan nasal spray.

5.3 Members reiterated their observation that clinical trials suggested that approximately 30% of patients do not respond to sumatriptan (or any other triptan) as a first-line agent but that a significant proportion of these patients will respond to a different triptan. The Committee noted that rizatriptan 10 mg wafers will be listed in the Pharmaceutical Schedule from 1 June 2008 to fill an unmet clinical need for a second funded triptan. The Committee considered that it would be useful to have rizatriptan 5 mg wafer but noted that this strength was not marketed in New Zealand.

5.4 The Committee noted that a proportion of patients (potentially 50%) would not respond to a second triptan. The Committee noted that, like tablet triptan formulations, rizatriptan wafers are absorbed through the gastrointestinal tract, which could reduce their efficacy in patients with severe nausea and vomiting. The Committee considered that if rizatriptan wafers were not swallowed with water but left to dissolve on the tongue, their

absorption and onset of action would likely be delayed compared with some tablet triptan formulations. The Committee considered that approximately 30% of a nasal spray would be absorbed in the nasal area, with the remainder likely being absorbed through the gastrointestinal tract and subject to the same reduced benefit for patients with severe nausea and vomiting.

5.5 The Committee considered that results from clinical trials supported the rapid absorption of zolmitriptan nasal spray claimed by the supplier. The Committee considered it likely that a more rapid absorption would translate into a faster onset of action clinically; however, the Committee noted that the evidence only supported this for zolmitriptan 5 mg nasal spray versus zolmitriptan 2.5 mg tablets and noted that no data had been provided comparing the onset of action of zolmitriptan 5 mg nasal spray with the equivalent dose of zolmitriptan tablets or other triptans.

5.6 The Committee considered that results of clinical trials showed that zolmitriptan 2.5 mg and 5 mg tablets were superior to placebo in the treatment of migraine, and that zolmitriptan 5 mg tablets were comparable in terms of efficacy and tolerability to sumatriptan 50 mg and 100 mg tablets. The Committee noted that studies suggested that most patients appeared to get the same benefit from zolmitriptan 2.5 mg tablets as from the 5 mg tablets. The Committee considered that rizatriptan 10 mg provides superior efficacy to zolmitriptan 2.5 mg and 5 mg.

5.7 The Committee considered that zolmitriptan 5 mg nasal spray would most benefit patients with migraine associated with severe nausea and vomiting who could not take tablets and who could not use a parenteral delivery form of other antimigraine treatments. The Committee considered that if it was listed without restrictions, zolmitriptan 5 mg nasal spray would be used instead of rizatriptan wafers and sumatriptan tablets, and in up to 50% of patients currently taking injection forms of sumatriptan and other antimigraine treatments.

5.8 The Committee considered that zolmitriptan 2.5 mg and 5 mg tablets would most benefit patients who did not respond to one or two other triptans. The Committee considered that zolmitriptan tablets would have more rapid absorption than rizatriptan wafers but that rizatriptan wafers would have some advantages over zolmitriptan tablets in patients with nausea and vomiting. The Committee considered that if rizatriptan wafers were swallowed with water they would be likely to have a similar time to onset of action as triptan tablets. The Committee considered that zolmitriptan 2.5 mg and 5 mg tablets would be used instead of rizatriptan wafers and sumatriptan tablets and would likely grow the triptan market overall if listed without restrictions. The Committee considered that listing zolmitriptan tablets would be unlikely to significantly reduce the use of non-triptan antimigraine treatments significantly.

5.9 The Committee considered that there was no clinical reason to place any restrictions on the use of zolmitriptan tablets or nasal spray. However, the Committee considered that if zolmitriptan nasal spray was listed in the Pharmaceutical Schedule it should be restricted, on the basis of cost, to patients who cannot take oral antimigraine treatments because of severe vomiting. The Committee noted that it would be relatively easy to access zolmitriptan under such a restriction.

5.10 The Committee noted that sumatriptan nasal spray was also registered, and appeared to be absorbed at a similar rate to zolmitriptan nasal spray but with better 2-hour response

rates. The Committee observed that there could be a potential cost from triptan nasal sprays through "trial fire" wastage, noting that zolmitriptan was a single-spray unit.

5.11 The Committee **recommended** that zolmitriptan 2.5 mg and 5 mg tablets be listed in the Pharmaceutical Schedule without restrictions only if cost-neutral to the Pharmaceutical Budget.

5.12 The Committee further **recommended** that zolmitriptan 5 mg nasal spray be listed in the Pharmaceutical Schedule only if cost-neutral compared with sumatriptan injection. The Committee noted that if zolmitriptan nasal spray was used in place of some other antimigraine treatments it could be a cost to the Pharmaceutical Budget. The Committee considered that one way to ensure that zolmitriptan nasal spray was used as an alternative to sumatriptan injection only would be to place a Special Authority restriction on both sumatriptan injection and zolmitriptan nasal spray.

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

6 Escitalopram (Lexapro) as an alternative to venlafaxine extended-release for the treatment of depression

6.1 The Committee considered an application from Lundbeck for the listing of escitalopram on the Pharmaceutical Schedule as an alternative to venlafaxine extended-release for the treatment of depression. The Committee noted that this was the fifth application from Lundbeck for the funding of escitalopram, and that the previous four applications (under various proposed criteria for the treatment of major depression, treatment-resistant depression, severe depression, and obsessive-compulsive disorder) had not received positive listing recommendations.

6.2 The Committee reiterated its previous view that there were no particular safety concerns with escitalopram and that it is well tolerated.

6.3 The Committee noted that the supplier had provided three new studies not seen before by the Committee. The first (Yevtushenko et al. Clin Ther 2007;29(11):2319-32) was a randomised, double-blind, active comparator-controlled 6-week study in 330 patients with major depressive disorder treated with escitalopram 10 mg, citalopram 10 mg or citalopram 20 mg. The results of this study showed that escitalopram 10 mg was significantly better than citalopram 20 mg in terms of mean change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, response rate, remission rate, and changes in Clinical Global Impression (CGI) scores. Escitalopram was also significantly better tolerated than citalopram. The Committee considered that this was a good quality study and supported the supplier's claim that escitalopram was superior to citalopram at equivalent doses.

6.4 The Committee considered that the second study (Lancon et al. Int J Psychiatry Clin Practice 2006;10(2):131-137), which compared escitalopram with citalopram in 127 patients with major depressive disorder, was of limited value because it was not randomised and there were differences between the treatment groups at baseline.

6.5 The third study (Montgomery & Andersen. Int J Psychopharmacol 2006;21:297-309) was a re-analysis of data from two published randomised controlled trials comparing escitalopram with venlafaxine in patients with major depressive disorder. The first trial referred to in the re-analysis (Mongomery et al. Neuropsychobioloy 2004;50:57-64) was conducted in primary care and compared escitalopram 10–20 mg with venlafaxine 75–150 mg. The second trial referred to in the re-analysis (Bielski et al. J Clin Psychiatry 2004;65:1190-1196) was conducted in a specialist setting and compared escitalopram 20 mg with venlafaxine 225 mg. Separately, these two studies showed that the two treatments had similar efficacy; however, the Committee noted that the doses of venlafaxine were low compared to the doses of escitalopram used, and that 225 mg was regarded as a relatively low dose of venlafaxine in the treatment of major depression. The Committee considered that at doses below 225 mg, venlafaxine behaved similarly to a selective serotonin reuptake inhibitor (SSRI) and that doses above this were required to obtain noradrenaline blockade. The Committee noted that the re-analysis of data from these studies appeared to suggest that there were some benefits of escitalopram over venlafaxine in patients with severe depression; however, the Committee considered that the evidence was not strong enough to conclude that escitalopram is superior to venlafaxine for severe depression.

6.6 The Committee considered that the evidence supported superior tolerability with escitalopram compared with venlafaxine. The Committee considered that this could translate into clinical benefits if it resulted in more patients being retained on maintenance treatment, although it noted there was no evidence presented to support this.

6.7 The Committee noted that venlafaxine is currently restricted to patients with treatment-resistant depression, which would be the relevant patient group if escitalopram were to be listed on the Pharmaceutical Schedule as an alternative to venlafaxine. The Committee considered that patients with treatment-resistant depression did not necessarily respond to treatment in the same way as patients with severe depression, and noted that the supplier had not provided any compelling data to suggest that escitalopram was as effective as venlafaxine in this patient group. The Committee considered that if patients were resistant to SSRIs it would make the most sense clinically to try another class of antidepressant (eg venlafaxine) rather than switching to escitalopram.

6.8 The Committee considered that the supplier had not provided sufficient evidence to support a listing of escitalopram as an alternative to venlafaxine given the current restrictions on venlafaxine and therefore **recommended** that the application to list escitalopram as an alternative to venlafaxine be declined. However, the Committee considered that on the basis of current evidence there was no clinical reason not to list escitalopram on the Pharmaceutical Schedule as an alternative to other SSRIs, and **recommended** a general listing of escitalopram in the Pharmaceutical Schedule with a low priority. The Committee noted that escitalopram was significantly more expensive than other SSRIs and considered that this should be taken into account when considering a listing of escitalopram.

6.9 The Decision Criteria relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

7 Naltrexone hydrochloride (ReVia) for treatment of alcohol dependence

7.1 The Committee noted correspondence from patient and clinician groups, including responses to consultation on recent changes to the naltrexone Special Authority, requesting changes to the current restrictions applying to naltrexone for the treatment of alcohol dependence. The Committee noted that the two key requested changes were to increase the amount of treatment permitted within a 12-month period and to widen access to naltrexone to prescribers in primary care.

7.2 The Committee noted that several correspondents cited the COMBINE study (Anton et al, JAMA 2006;295:2003-2017) in support of their request to widen access to naltrexone in primary care, specifically pointing to the benefits achieved from the use of naltrexone without intensive, comprehensive counselling. The COMBINE study was a randomised, double-blind study in 1,383 patients, the aim of which was to compare outcomes after 16 weeks of treatment with naltrexone or acomprosate or both medications and/or placebo in combination with medical management, with or without combined behavioural intervention (CBI). After 16 weeks of treatment, patients who received medical management plus naltrexone had better drinking outcomes than those who received medical management plus placebo, regardless of whether or not patients also received CBI.

7.3 The Committee noted that the results of a more recent publication from the COMBINE trial (Donovan et al, J Stud Alcohol Drugs 2008;69:5-13), which reported outcomes one year after the end of treatment, suggested that CBI conferred additional benefit over medical management over the follow-up period, with patients receiving medical management and CBI being 20% more likely to be classified as having a good clinical response than those who received medical management without CBI. The Committee noted that this effect emerged after the 16-week active treatment period. The Committee noted that patients taking naltrexone (regardless of what other therapy was also taken) had a significantly higher percentage of abstinent days than placebo groups with no CBI, and that patients taking CBI without any pharmacotherapy also had a significantly higher percentage of abstinent days than placebo groups with no CBI. The Committee considered that the results of this study supported the importance of a comprehensive treatment program for alcohol dependence in the use of naltrexone and **recommended** against altering this aspect of the naltrexone Special Authority.

7.4 The Committee reviewed a recent study investigating outcomes in 146 alcohol-dependent patients following 24 weeks' continuous treatment with naltrexone or 12

weeks' treatment with naltrexone followed by 12 weeks of placebo (Davidson et al, Psychopharmacology 2007;194:1-10). The Committee noted that no differences were observed between treatment groups in terms of percent days abstinent or percent heavy drinking days at the end of the study, and that compliance decreased during weeks 13-24 regardless of whether patients were taking placebo or naltrexone. The Committee considered that there was no compelling evidence to support an increase in the amount of subsidised naltrexone permitted in a 12-month period and **recommended** against altering this aspect of the naltrexone Special Authority.

7.5 The Decision Criteria relevant to these recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

8 Tramadol economic analysis

8.1 The Committee reviewed a rapid economic analysis provided by PHARMAC staff on tramadol for the treatment of acute and chronic pain. The Committee noted that tramadol had been assessed on several occasions by PTAC and the Analgesic Subcommittee of PTAC, and that it had been included in the recent Invitation to Tender for potential listing in the Pharmaceutical Schedule. The Committee noted that in December 2006 the Analgesic Subcommittee had recommended listing tramadol with a medium priority, and that PTAC had noted and accepted this minute at its meeting in February 2007 and had requested that it be presented with a cost-utility analysis.

8.2 The Committee considered that the relative potencies and average daily doses for comparator treatments used in the analysis were appropriate.

8.3 The Committee noted that at current pricing (in Section H of the Pharmaceutical Schedule), and based on advice from the Analgesic Subcommittee regarding the relative dose and potency of tramadol compared with opioid analgesics, tramadol would be cost-saving to the Pharmaceutical Schedule. The Committee noted that the price of tramadol was likely to reduce further through the 2007/08 tender.

8.4 The Committee noted that tramadol was being used extensively in hospitals, and was funded by the Accident Compensation Corporation and Work and Income New Zealand.

8.5 The Committee considered that there was no reason not to award a tender for tramadol. The Committee considered that it would be important to have the sustained-release preparations available because the side effect of nausea was reduced with sustained-release preparations. The Committee also considered that it would be useful to have the liquid and injection preparations available in the future.

8.6 The Committee **recommended** that this be progressed with high priority.

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

9 Dipyridamole for the secondary prevention of stroke and transient ischaemic attack

9.1 The Committee reviewed additional information provided by Boehringer Ingelheim and a letter from the Stroke Foundation in support of funding of extended release dipyridamole as a first-line treatment in the secondary prevention of stroke and transient ischaemic attacks (TIA).

9.2 The Committee noted that it had previously considered applications for dipyridamole for the secondary prevention of stroke and TIA on a number of occasions, the most recent being in February 2007.

9.3 The Committee noted that the new information provided included the Australian National Stroke Foundation 2007 Clinical Guidelines for Acute Stroke Management and information regarding the bioequivalence of available brands of dipyridamole.

9.4 The Committee noted that since it last reviewed dipyridamole, the 2006 Cochrane review "Dipyridamole for preventing stroke and other vascular events in patients with vascular disease" had been updated (April 2007). The Committee noted that in the review a comparison of dipyridamole with control (the presence or absence of other antiplatelet drugs) found that there was no evidence that dipyridamole had any effect on vascular death in patients presenting with vascular disease. However, there was a reduction in vascular events in patients presenting with cerebral ischaemia who received at least 400 mg per day of dipyridamole. In addition, the Committee noted that for combination treatment (dipyridamole plus aspirin versus aspirin alone) the review reported a reduction in vascular events although there was no reduction in vascular deaths.

9.5 The Committee noted that there is a difference between the tablet strengths that were used in recent trials and those that are currently funded.

9.6 The Committee noted that the Australian National Stroke Foundation (ANSF) 2007 Guidelines recommended that low-dose aspirin and modified-release dipyridamole should be prescribed to all people with ischaemic stroke or TIA who do not have concomitant acute coronary disease. The Committee noted that the recommendations by ANSF were based on information that PTAC had previously considered.

9.7 The Committee **recommended** that the combination dipyridamole plus aspirin preparation should not be listed on the Pharmaceutical Schedule since the aspirin dose

contained in the combination tablet is not the recommended dose, and more importantly, because a number of patients are likely to discontinue combination therapy due to intolerance and that this may result in these patients taking no antiplatelet therapy.

9.8 The Committee considered that its February 2007 comments and recommendation, as follows, were appropriate.

9.8.1 "The Committee considered that the evidence supporting combined therapy (aspirin and dipyridamole) was weak and that the side-effects and the price of combined therapy were significant when compared to aspirin alone. As a result the Committee recommended that the application to list Persantin and Asasantin be declined."

9.9 The Committee noted that information regarding the bioequivalence of the available brands of dipyridamole had been provided by the supplier, which indicated that different amounts of dipyridamole were released from each brand under two different pH conditions (4.5 and 6.0). The Committee noted that the bioequivalence studies are conducted in young people taking no other treatments and that there may be a potential problem with the bio-availability of the listed preparation in elderly patients taking proton pump inhibitors. However, the Committee also noted that the Generics Subcommittee was aware of this information in 2003 when it concluded that the pharmacokinetic parameters defining bioavailability (AUC, Cmin, Cmax, and DF) were not different between the brands and that the Generics Subcommittee considered them to be bioequivalent.

9.10 The Committee noted that there were additional issues relevant to the listing of dipyridamole in the Pharmaceutical Schedule including the place of clopidogrel in the treatment of stroke and TIA patients, the registered indications of the available brands, the appropriate dose, and the available options for patients intolerant of aspirin.

9.11 The Committee reiterated its February 2007 recommendation that the current Dipyridamole Special Authority be removed. The Committee recommended that these changes occur as soon as possible.

10 Transfusion-related iron overload – deferasirox (Exjade)

10.1 The Committee reviewed additional information supplied by Novartis relating to its application for the listing of deferasirox (Exjade) on the Pharmaceutical Schedule for the treatment of patients with transfusional chronic iron overload due to congenital anaemias or acquired anaemia relating to malignancy.

10.2 The Committee noted that this pharmaceutical was a tablet and that it had previously considered the listing of deferasirox in July 2006.

10.3 The Committee noted that desferrioxamine is currently listed in the Pharmaceutical Schedule, and that the benefit of deferasirox treatment compared with desferrioxamine is the oral mode of administration and the potential for improvement in compliance.

10.4 The Committee considered that there was an unmet clinical need for patients who experience treatment-limiting adverse effects with the administration of desferrioxamine (subcutaneous infusion), those who have contraindications to desferrioxamine, and children with congenital anaemias where the subcutaneous infusion would be associated with complications related to decreased surface area for infusion sites.

10.5 The Committee noted that the additional information supplied by Novartis relating to deferasirox included targeting criteria developed in conjunction with New Zealand haematologists taking into account post-marketing surveillance data. The Committee noted that there is no further published information regarding the efficacy of deferasirox since the Committee last reviewed the application.

10.6 The Committee noted that Novartis proposed three patient groups. The first patient group and those with the highest priority being patients with congenital inherited anaemias; the second group being patients with acquired anaemias who develop iron overload secondary to stem cell transplant (SCT), myelodysplastic syndrome (MDS) or bone marrow transplant; and the third patient group being all patients with acquired anaemias who are eligible under the current registered indications.

10.7 The Committee considered that the July 2006 minutes may not accurately reflect the patient groups that the Committee considered appropriate at the time. The Committee gave a high priority for use of deferasirox only in children with congenital inherited anaemias.

10.8 The Committee considered that there is sufficient evidence to support the use of deferasirox in patients with congenital inherited anaemias such as beta-thalassaemia major and sickle cell anaemia as a first-line or second-line agent.

10.9 The Committee considered that evidence for the use of deferasirox in patients with acquired anaemias such as SCT and MDS who develop iron overload is not strong and that the inclusion of MDS patients would have a significant budgetary impact. However, the Committee also noted that there are several trials underway that investigate the use of deferasirox in patients with SCT and MDS and considered that the results of these studies should be reviewed once available.

10.10 The Committee noted that Periodic Safety Report 4 (1 May 2007 to 31 October 2007) had been supplied and that additional adverse events had been reported since PTAC reviewed deferasirox in July 2006. These included renal impairment, acute renal failure, cytopenias, agranulocytosis, liver function abnormalities and gastrointestinal side-effects. The Committee noted that the long-term adverse effects of deferasirox are not clear and that its safety is being closely monitored overseas.

10.11 The Committee noted the high incremental cost of deferasirox compared with desferrioxamine, and that listing would be associated with a fiscal risk.

10.12 The Committee noted the PHARMAC review of the supplier analysis, and that the cost per QALY results largely depended on the utility gain from oral treatment and the incremental cost compared with desferrioxamine. The Committee considered that targeting patients with persistent intolerance or contraindication to desferrioxamine would ensure that listing was restricted to the group of patients for whom treatment was most likely to be cost-effective.

10.13 The Committee considered the appropriate weight estimate for patients with congenitally inherited anaemias to be 54 kg and for acquired anaemias to be 70 kg.

10.14 The Committee considered that access to deferasirox should be limited by Special Authority and **recommended** that deferasirox be listed with a high priority for patients (children and adults) with chronic transfusional iron overload due to congenital inherited anaemias where desferrioxamine is not tolerated or contraindicated.

10.15 The Decision Criteria relevant to the high recommendation for deferasirox are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

11 Nilotinib (Tasigna) for second-line treatment of patients with imatinib resistant, or intolerant, chronic myeloid leukaemia

11.1 The Committee reviewed an application from Novartis New Zealand for the listing of Nilotinib (Tasigna) on the Pharmaceutical Schedule for the treatment of patients with imatinib-resistant or imatinib-intolerant, chronic or accelerated phase, chronic myeloid leukaemia (CML).

11.2 The Committee noted that imatinib-resistant patients currently have limited treatment options. Members noted that imatinib is currently funded for patients with CML at doses of up to 400 mg/day in chronic phase or 600 mg/day in the accelerated or blast phase. Members noted that currently the cost of treating approximately 300 CML patients in New Zealand is approximately $10 million annually, which is about a fifth of the total spend on all other cancer treatments combined.

11.3 Members noted that the review of funding applications for increased dosing of imatinib (up to 600 mg/day) for patients with chronic phase CML, and the listing of dasatinib (Sprycel) for patients with imatinib-resistant or imatinib-intolerant, accelerated or blast phase, CML, were ongoing.

11.4 The Committee noted that nilotinib is an oral tyrosine kinase inhibitor, derived from imatinib, selective for BCR-ABL. Members noted that nilotinib is metabolised by the cytochrome P450 3A4 (CYP3A4) metabolic pathway and that absorption is affected by food, with the bioavailability of nilotinib increased (higher C_{max}) by foods that inhibit CYP3A4.

11.5 The Committee considered that the quality of evidence provided was poor. The Committee noted that the supplier's key evidence was from a single open-label non-randomised phase II study of nilotinib (Study 2101) conducted across various patient

cohorts. Members noted that there were no direct comparative studies of nilotinib with relevant comparators, such as dasatinib or high dose imatinib.

11.6 The Committee reviewed data from two publications derived from Study 2101. The first publication (Kantarjian et al Blood 2007; 110: 3540-6) reported data from 280 patients with imatinib-resistant or imatinib-intolerant, chronic phase CML. The second publication (Le Coutre et al Blood 2008; 111: 1834-9) reported data from 119 patients with imatinib-resistant or imatinib-intolerant, accelerated phase CML. Members noted that in these studies nilotinib was dosed at 400 mg twice daily; however, the dose could be increased to 600 mg twice daily if patients had not achieved a Haematological Response (HR) by three months, or a Cytogenetic Response (CyR) by six months, or a Major Cytogenetic Response (MCyR) by 12 months. Data was reported in patients who had received at least six months of nilotinib treatment. Members noted that the majority of patients had received more than 600 mg/day imatinib prior to study entry, a dose higher than is currently funded for imatinib.

11.7 The Committee noted that in the Kantarjian study of chronic phase CML patients, 134 patients (48%) achieved the primary endpoint of a MCyR, with 88 (31%) patients achieving Complete CyR and 46 (16%) achieving a Partial CyR. The median time to MCyR was 2.8 months and of those who achieved a McyR 96% continued treatment and had not progressed at six months. Members noted that data for 38 chronic phase CML patients enrolled in this study were not presented because they had not been treated with nilotinib for six months.

11.8 The Committee noted that the main adverse reactions to nilotinib in the Kantarjian study were rash (28%), nausea (24%) pruritis (24%) and fatigue (19%), with 42 patients withdrawing due to adverse reactions. Seventeen patients required discontinuation of treatment due to neutropaenia (n=9) or thromocytopaenia (n=8)

11.9 The Committee noted that in the Le Coutre study of accelerated phase CML patients, 31 (26%) patients achieved the primary endpoint of a CHR, with 35 (29%) patients achieving MCyR and 19 (16%) achieving a Complete CyR. Members considered that the efficacy of nilotinib was not as good in this population compared with the chronic phase CML patients reported by Kantarjian. Members considered that the adverse reactions were similar to those reported by Kantarjian but with higher rates of haematological toxicities with 35% of patients developing grade 3/4 thrombocytopaenia, 21% neutropaenia and 13% anaemia.

11.10 The Committee noted that nilotinib may be associated with cardiotoxicity. Members also noted that the presence of the majority of BCR-ABL mutations did not appear to affect nilotinib efficacy unlike imatinib.

11.11 The Committee considered that nilotinib was efficacious in imatinib-resistant/intolerant patients and that it may have greater potency than dasatinib or high-dose imatinib; however, the absence of comparative trials limited this assumption and data was limited with short follow-up.

11.12 The Committee considered that the cost of nilotinib was high and that a key assumption of the supplier, namely that patients currently resistant or intolerant of imatinib are continuing with imatinib treatment, was incorrect and therefore the cost would be increased compared with the suppliers estimates.

11.13 The Committee **recommended** that the application for funding of nilotinib be declined due to its limited, short-term data and high cost. Members recommended that this minute and key papers be provided to the Cancer Treatments Subcommittee (CaTSoP) for comment.

11.14 The Decision Criteria relevant to this recommendation are: (*i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

12 Insulin glargine (Lantus) for type 2 diabetes

12.1 The Committee considered an application from Sanofi Aventis to widen access to insulin glargine (Lantus), as listed on the Pharmaceutical Schedule, to include the treatment of type 2 diabetes. The Committee noted that insulin glargine was an insulin analogue, equipotent to human insulin.

12.2 The Committee noted that the application proposed that insulin glargine would be listed on the Pharmaceutical Schedule subject to the Special Authority criteria:

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

1. Treatment of patients with Type 2 diabetes in whom HbA1c targets <7% have not been reached despite maximal oral drug and/or insulin therapy or
2. Either:
    - 2.1 Patient has experienced more than one unexplained severe hypoglycaemic episode in the previous 12 months (severe defined as requiring the assistance of another person); or
    - 2.2 Patient has experienced unexplained symptomatic nocturnal hypoglycaemia, biochemically documented at <3.0 mmol/L, more than once a month despite optimal management.

Renewal only from a relevant specialist or general practitioner.
Approvals valid for one year for applications meeting the following criterion:

1. Patient is experiencing better glycaemic control or
2. Fewer hypoglycaemic events than the period prior to initiation of therapy with insulin glargine.

12.3 The Committee noted the key evidence of efficacy provided in the form of eight randomised open label trials versus NPH insulin, one randomised open label trial versus pre-mixed regular/NPH insulin, seven observational studies, and three of the most

recently published systematic reviews on insulin glargine. The Committee noted that overall the trials showed a reduction in hypoglycaemia, in particular nocturnal hypoglycaemia. The Committee considered that the strength of the evidence was moderate and that the quality of the evidence was poor to moderate.

12.4 The Committee noted that overall, the trials showed that insulin glargine had similar efficacy and a reduction in hypoglycaemia, in particular in nocturnal hypoglycaemia compared with NPH insulin. The Committee noted that while the relative reductions in hypoglycaemia compared with NPH were larger than those seen in patients with type 1 diabetes, the absolute reductions were small. The Committee considered that there was no long-term efficacy and safety data as evidenced in the reviews by Horvath et al (2007)[1] and Clissold (2007)[2].

12.5 The Committee considered that insulin glargine had a similar effect to NPH insulin; however, it noted that it is a long-acting insulin with a flat action profile. The Committee considered that, if access was widened as proposed, insulin glargine would be used with oral hypoglycaemic agents and short or and rapid-acting insulins. The Committee considered that insulin glargine would substitute for NPH insulins and potentially for mixed preparations.

12.6 The Committee considered that hypoglycaemia is not a major issue for the majority of type 2 diabetic patients; however, it is a problem for type 2 diabetic patients on intensive regimes including insulin, who can experience troublesome hypoglycaemic episodes.

12.7 The Committee considered that the average daily dose of insulin glargine, which for type 1 patients was 26.8u, would be significantly higher for type 2 patients. The Committee noted that the trials used a dose range from 23u to 68u per day and that in four trials they used at least 40u per day.

12.8 The Committee noted the current usage of insulin glargine for type 1 patients and compared it with the projected usage described in the supplier's original application. The Committee noted that the supplier claimed that insulin glargine would be used second-line after other available insulins. However, the Committee considered that the proposed Special Authority criteria would allow insulin glargine to be used widely in patients with type 2 diabetes and that it would be used in preference to other insulins. Members considered that targeting access would be difficult and that this posed a very high fiscal risk.

12.9 The Committee considered that there was no clinical reason not to fund insulin glargine for patients with type 2 diabetes; however, the Committee considered that widening access as proposed could have a significant fiscal impact. Therefore, the Committee **recommended** that the application to widen access to insulin glargine to type 2 patients on the Pharmaceutical Schedule be declined at this time. The Committee noted that the minute should be referred to the Diabetes Subcommittee of PTAC.

12.10 The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing*

[1] Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD005613.
[2] Core Evidence 2007;292):89-110

medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, and *(vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

13 5-second Optium Blood Glucose Test Strip

13.1 The Committee considered an application from Medica Pacifica for a new generation of Optium blood glucose test strips to be listed on the Pharmaceutical Schedule at the same price, and under the same restrictions, as the current Optium blood glucose test strips.

13.2 The Committee noted that the supplier had submitted an application for a three second strip in November 2007 and that this had been accepted for listing on the Pharmaceutical Schedule. Members noted that the supplier now preferred to align supply with the same test strip as that used in Australia.

13.3 Members noted that the new test strip was compatible with the Optium and Optium Exceed blood glucose meters currently listed on the Pharmaceutical Schedule; therefore, patients would not be required to change meters with the introduction of the new generation Optium blood glucose test strips.

13.4 The Committee noted that the new generation Optium test strip appeared to have some advantages over the existing Optium test strip; namely, it requires less blood (0.6uL rather than 1.5uL) and gives quicker results (5 seconds rather than 10 seconds).

13.5 The Committee noted the test results for the new generation of Optium blood glucose test strips from the Clinical Pathology Department of Auckland City Hospital. The Committee considered that the average imprecision of 7.7% was acceptable. The Committee considered that the average bias of +13.1% was acceptable.

13.6 The Committee **recommended** that the application be referred to the Diabetes Subcommittee of PTAC for consideration. Members considered that, subject to the Diabetes Subcommittee of PTAC agreement, the Committee did not have any reservations regarding the listing of the new generation of Optium blood glucose test strips on the Pharmaceutical Schedule.

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

14 Sitagliptin (Januvia) for type 2 diabetes

14.1 The Committee considered an application from Merck Sharpe and Dohme to list sitagliptin (Januvia) on the Pharmaceutical Schedule. The Committee noted that sitagliptin was a dipeptidyl peptidase (DPP-4) inhibitor used in the treatment of patients with type 2 diabetes.

14.2 The Committee noted that the application proposed that sitagliptin be listed on the Pharmaceutical Schedule subject to similar Special Authority criteria as currently applied to pioglitazone.

14.3 The Committee noted that sitagliptin had a unique mode of action.

14.4 The Committee noted the key trials comparing sitagliptin with other oral treatments currently used in the treatment of patients with type 2 diabetes: three key trials (Ascher et al, Raz et al and Scott et al) that considered the benefit of sitagliptin monotherapy (with placebo as comparator) and six key trials (Rosenstock et al, Charbonnel et al, Nauck et al, Hermansen et al, Goldstein et al and Scott et al) that considered the benefit in combination with other treatment regimens for patients with type 2 diabetes.

14.5 The Committee noted that in the key trials, sitagliptin showed modest efficacy and was generally associated with a modestly favourable weight change profile. The Committee noted that sitagliptin appeared to be associated with fewer hypoglycaemic episodes than sulphonylureas.

14.6 The Committee considered that there was limited long-term safety data. Members considered that as sitagliptin was a novel drug with a novel mechanism of action, there was the potential for unexpected consequences. The Committee noted the long-term consequences that have emerged with glitazones (such as an increase in fractures), which emphasises the importance of long-term safety data.

14.7 The Committee considered the question of the appropriate place in therapy of sitagliptin, which is currently unclear. The Committee noted that the only long-term study (52 weeks) provided (Nauck et al) showed that maximal efficacy in lowering HbA1c and Fasting Plasma Glucose was observed at 24 to 30 weeks with both sitagliptin and glipizide.

14.8 [withheld under sections 9(2)(b)(ii) and 9(2)(j) of the OIA] The Committee considered that the incremental benefits, as seen in the clinical data, were unlikely to justify the additional cost of sitagliptin.

14.9 The Committee noted the cost-utility analysis provided by the supplier comparing treatment with sitagliptin plus metformin to treatment with pioglitazone plus metformin. The Committee noted that PHARMAC staff had amended several cost inputs in the analysis to reflect current clinical practice and expected price reductions. The Committee noted that these amendments increased the cost per quality-adjusted life year (QALY) of sitagliptin.

14.10 The Committee **recommended** that the application to list sitagliptin on the Pharmaceutical Schedule be declined at this time. The Committee noted that the

application and PTAC minute should be forwarded to the Diabetes Subcommittee for comment.

14.11 The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services,* and *(vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

15 Rituximab (MabThera) for rheumatoid arthritis

15.1 The Committee considered a re-submission from Roche Products (NZ) Limited for the listing of rituximab (Mabthera) for patients with severe, active rheumatoid arthritis (RA) who have had an inadequate response, or intolerance to prior treatment with a tumour necrosis factor antagonist (anti-TNF), and for patients in whom an anti-TNF is contraindicated or inappropriate.

15.2 The Committee noted that it had considered an application from Roche Products and the New Zealand Rheumatology Association (NZRA) for the listing of rituximab for RA at its November 2007 meeting. The Committee noted that the re-submission included a cost-minimisation analysis based on comparative effectiveness drawn from indirect comparisons of rituximab, adalimumab and etanercept for this indication.

15.3 The Committee noted that there had been one Phase III, randomised, placebo-controlled study assessing the efficacy of rituximab for patients who had previously failed treatment with one or more TNF-inhibitors (The REFLEX-study, Cohen et al 2006). Patients were randomised to receive either 1000 mg rituximab on days 1 and 15 or placebo, in combination with methotrexate and corticosteroids. The primary efficacy response (ACR20 at 24 weeks) rates were significantly higher in the rituximab treated patients compared with placebo (51% vs 18%); secondary efficacy endpoints of ACR50 and ACR70 were also higher in the rituximab treated patients (27% vs 5% ACR50, and 12% vs 1% ACR70). The mean time to re-treatment was 10.6 months.

15.4 The Committee noted that there have been no head-to-head clinical trials directly comparing the efficacy of rituximab with adalimumab or etanercept for RA. Therefore, methotrexate was used in the re-submission as the common reference to make an indirect comparison possible. The re-submission included two studies for etanercept plus methotrexate versus placebo plus methotrexate (Weinblatt et al 1999 and Klareskog et al 2004) and three studies of adalimumab plus methotrexate versus placebo plus methotrexate (Weinblatt et al 2003, Furst et al 2003, Keystone et al 2004) for treatment of patients with severe RA who have failed to respond to previous disease-modifying anti-rheumatic drugs (DMARDS). The efficacy parameters in the studies were primarily based on the criteria from the American College of Rheumatology (ACR). The Committee also considered a meta-analysis undertaken by the supplier comparing these studies to the REFLEX study on rituximab (Cohen et al 2006) for patients who had failed treatment with an anti-TNF agent. The results of the meta-analysis indicated that

rituximab was likely to be as effective as etanercept or adalimumab in terms of ACR20, ACR50 and ACR70 response rates.

15.5 The Committee considered that the evidence available indicates that rituximab is at least as effective as a TNF-inhibitor for the treatment of RA following failure of treatment with an initial TNF-inhibitor.

15.6 The Committee noted that the cost-minimisation analysis provided by Roche indicated that rituximab is cost-saving compared with etanercept and adalimumab. The Committee noted that, in the absence of other options, it was likely that patients were remaining on adalimumab and could potentially have greater improvement on rituximab.

15.7 The Committee noted that PHARMAC had undertaken a rapid cost-utility analysis on rituximab. This analysis was based on the assumption that patients not receiving an adequate response to adalimumab would not continue to receive treatment under the Special Authority criteria, and therefore the appropriate comparator was considered to be placebo. The Committee noted that this analysis indicated that the cost per quality-adjusted life of rituximab was highly likely to be over $100,000.

15.8 The Committee considered that the time until re-treatment with rituximab in clinical practice may be longer than the time until re-treatment reported in the clinical trials (average of 10.6 months). The Committee considered that early re-treatment (e.g. within six months of the previous treatment) could be prevented by appropriate renewal criteria for a Special Authority.

15.9 The Committee noted that there is currently no other funded option for patients who do not respond to treatment with an anti-TNF. The Committee noted that some DHBs are currently funding rituximab for patients who do not respond or are intolerant to adalimumab, resulting in inconsistent access to treatment.

15.10 The Committee noted that further trials need to be conducted to determine the optimal dose of rituximab in RA. There has been only one study (Emery et al 2006) comparing different doses of rituximab in RA and no data presented on the effect of a single infusion of rituximab.

15.11 The Committee **recommended** not to change the previous recommendation that rituximab be listed in the Pharmaceutical Schedule with a medium to high priority.

15.12 The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*