

PTAC meeting held on 7 & 8 November 2013

(minutes for web publishing)

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

Note:

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

**Record of the
Pharmacology and Therapeutics Advisory
Committee Meeting**

Held on 7 & 8 November 2013

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1 Matters Arising

1.1 Rituximab Consultation Responses

1.1.1 The Committee noted a paper from PHARMAC staff seeking the Committee's view on a number of issues raised in response to PHARMAC's recent consultation on a proposal to list rituximab on the Hospital Medicines List for various haematological conditions.

1.1.2 The Committee considered consultation responses and additional information from PHARMAC staff in relation to the restrictions proposed for rituximab for the following indications:

- Immune Thrombocytopenic Purpura (ITP);
- Thrombotic thrombocytopenic purpura (TTP);
- Pure red cell aplasia (PRCA); and
- ANCA vasculitis

Each of these indications was discussed separately as follows:

Immune Thrombocytopenic Purpura (ITP)

1.1.3 The Committee noted requests to remove the requirement for splenectomy as a pre-requisite prior to rituximab funding. Members noted that international guidelines were not consistent in their recommendations for second line treatment. Members noted that the American Society of Haematologists 2011 guidelines recommended second line splenectomy for patients who have failed corticosteroids or rituximab, second line for patients at risk of bleeding who have failed one line of therapy such as corticosteroids, IV-Ig or splenectomy, whilst the International Consensus Report suggested either rituximab or splenectomy as appropriate second line treatment options. Members noted the results of a survey of NZ Haematologists provided by one of the responders indicated that 45% (15/33) thought the need for prior splenectomy was "not at all reasonable," while 55% (18/33) thought they could "live with it" or that it was "entirely appropriate". Members considered it was likely that over time guidelines would recommend rituximab as the preferred second line treatment option with splenectomy moved to third line.

1.1.4 The Committee noted that although splenectomy was associated with an initial higher response rate of approximately 80% compared with around 60% for rituximab, it would be associated with increased morbidity from surgery. Members considered that, they had insufficient information to recommend second line rituximab treatment over splenectomy at this time. Members did not recommend any change to this part of the restriction.

- 1.1.5 The Committee noted requests to amend the requirement for a platelet count of $< 20 \times 10^9/L$ to $< 30 \times 10^9/L$ for rituximab treatment initiation. Members agreed that a platelet count of $< 30 \times 10^9/L$ was consistent with severe disease and an increased risk of bleeding, therefore **recommended** this part of the restriction be amended accordingly.
- 1.1.6 The Committee noted requests to shorten the length of time required for rituximab retreatment from an initial response lasting at least 12 months. Members considered there was good evidence that most patients with a durable complete response to initial treatment (> 12 months) would respond to rituximab re-treatment if they subsequently relapsed, however, there was little evidence to support shortening this timeframe. Members did not recommend any change to this part of the restriction.

Thrombotic thrombocytopenic purpura (TTP)

- 1.1.7 The Committee noted requests to amend the criterion "2. Clinical response to plasma exchange was suboptimal or plasma exchange is contraindicated". Members noted that British Committee for Standards in Haematology 2012 guidelines for management of TTP and other thrombotic microangiopathies recommend corticosteroids as first line treatment, alongside plasma exchange with rituximab as a second line agent for refractory or relapsing disease, or as part of first line triple therapy in patients presenting with neurological and/or cardiac pathology.
- 1.1.8 The Committee **recommended** the criteria be amended to read "2. Patient has refractory or relapsing disease despite plasma exchange or plasma exchange is contraindicated."

Pure red cell aplasia (PRCA)

- 1.1.9 The Committee noted requests to extend funding for rituximab to include treatment of PRCA, and indication that was not included in the initial proposal.
- 1.1.10 The Committee noted that the request for funding was limited to PRCA secondary to chronic lymphocytic leukaemia (CLL). Members noted that whilst rituximab was funded for CLL the group of patients with PRCA would not meet the current requirements for initiation of rituximab treatment for CLL. The committee reviewed evidence from a number of publications that suggest that rituximab treatment would be useful, however, members considered that the evidence was likely subject to considerable publication bias and was based on very small patient numbers.
- 1.1.11 The Committee considered that it was unlikely that better evidence would be forthcoming and, given that the number of patients with PRCA accessing rituximab would likely be low, considered it reasonable to list rituximab in the HML for these patients in line with its use in hospitals prior to 1 July 2013. The Committee **recommended** rituximab be listed on the HML for PRCA patients subject to restriction as follows:

Initiation - PRCA – Haematologist.

Limited to 6 cycles

PRCA considered to be autoimmune and associated with a demonstrable B-cell lymphoproliferative disorder.

ANCA vasculitis

- 1.1.12 The Committee noted requests to remove the requirement for patients with MPO-ANCA vasculitis to have failed prior treatment with mycophenolate mofetil (MMF). Members considered it reasonable to keep this requirement noting moderate evidence of effect of MMF in MPO-ANCA vasculitis compared with cyclophosphamide from two small studies, Hu et al 2007 and Silva et al 2010.
- 1.1.13 The Committee noted requests to amend the length of treatment time requirement for a previous trial of cyclophosphamide. Members noted one respondent requested the length of time be increased as in their view cyclophosphamide often only works after 4 months and may take up to 6 months, whereas another respondent wished for this to be decreased suggesting that few patients would respond after 6 months if they failed to achieve remission at 3 months.
- 1.1.14 Members considered that it was reasonable to provide some flexibility in the criteria to enable clinicians to use their judgement regarding appropriate length of cyclophosphamide treatment and enable those who have truly progressive, unresponsive disease to have the option of changing to rituximab. The Committee **recommended** amending criterion 4.1 and 4.2 as follows:
- 4.1 Induction therapy with daily oral or pulse intravenous cyclophosphamide has failed to achieve complete absence of disease after **at least** 3 months; or
 - 4.2 Patient has previously had a cumulative dose of cyclophosphamide >15g or a further repeat 3 month induction course of cyclophosphamide would result in a cumulative dose >15g; or
- 1.1.15 The Committee noted a request that the cyclophosphamide contraindication criteria be amended to include males who wish to preserve their fertility when sperm banking is unavailable, unsuccessful or unacceptable. Members noted that cyclophosphamide was known to affect male fertility, however, in some centres sperm banking prior to cytotoxic treatment was funded. Members had sympathy for patients for whom sperm banking was not an option however considered that if the criteria were amended as proposed it would be associated with significant financial risk as effectively it could result in all male patients bypassing the requirement to have tried cyclophosphamide prior to rituximab.
- 1.1.16 The Committee noted a request to amend the wording “patient is a woman of childbearing age” to “females of child-bearing potential” in order to more clearly cover adolescents who are also of child bearing

potential. Members agreed, and **recommended** this change be made throughout the Pharmaceutical Schedule.

1.1.17 The Committee considered a request to allow funding of an alternative dose of rituximab under the restriction, namely a fixed dose of 1000 mg two weeks apart, rather than just 375 mg/m² of body-surface area per week for a total of 4 weeks. The Committee considered that although the evidence for 1000 mg dosing is weaker, it is less wasteful, and therefore it was reasonable to leave the decision up to the individual treating clinician. The Committee **recommended** that the criteria be amended to include the option of using a fixed dose of 1000 mg two weeks apart.

1.1.18 The Committee noted a request to fund rituximab for maintenance therapy. Members noted that although initial evidence for maintenance therapy was encouraging more evidence was needed and studies were underway. The Committee noted it would welcome a funding application once evidence from these studies was available.

2 Subcommittee Minutes

2.1 Mental Health Subcommittee – 15 July 2013

2.1.1 The Committee noted and accepted items 1 to 12, excepting the recommendation in relation to paliperidone depot injection in item 4.11.

2.1.2 Taking into account all the available evidence and the view of the Mental Health Subcommittee, the Committee reiterated its previous recommendation that paliperidone depot injection be listed on the Pharmaceutical Schedule only if it was cost-neutral or cost-saving versus risperidone depot injection.

2.2 Special Foods Subcommittee teleconference – 5 September 2013

2.2.1 The Committee noted and accepted the record of the Special Foods Subcommittee teleconference of 5 September 2013.

2.3 Ophthalmology Subcommittee teleconference – 2 May 2013

2.3.1 The Committee noted and accepted the record of the Ophthalmology Subcommittee teleconference of 2 May 2013.

3 Correspondence

3.1 Correspondence from Janssen-Cilag Pty Ltd. regarding Bortezomib (Velcade) retreatment for multiple myeloma.

3.1.1 The Committee noted the points raised in the letter.

3.1.2 Correspondence from Janssen-Cilag Pty Ltd, regarding abiraterone (Zytiga) in the Minutes of the August 2013 meeting.

3.1.3 The Committee agreed to amend 9.5.1 by replacing Patients with **People**, and to amend 9.12 by inserting **eventual** before chemotherapy.

4 Pertussis

Application

The Committee reviewed a request for information from PHARMAC staff regarding two component pertussis vaccine versus three component pertussis vaccine.

Recommendation

- 4.1 The Committee **recommended** that PHARMAC not change to a two component pertussis vaccine at this time.
- 4.2 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, (v)The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health & disability support services.*

Discussion

- 4.3 The Committee noted that PHARMAC had included the hexavalent infant vaccine in the Request for Proposals (RFP) for the National Immunisation Schedule released in June 2013. One proposal for the hexavalent vaccine had included a currently unregistered 2-component acellular pertussis (aP) vaccine. The Committee noted that PHARMAC was seeking advice on the acceptability of a 2-component pertussis vaccine for the New Zealand market.
- 4.4 The Committee noted that *Bordetella pertussis*, a small, gram-negative, pleomorphic bacillus, causes pertussis which is highly transmissible in family and health care settings. The Committee noted that the intent of vaccination is to protect those at greatest risk of severe sequelae or death, namely children under the age of one year. The Committee noted that pertussis is endemic in New Zealand and could not be eradicated by vaccination.
- 4.5 The Committee noted that the current funded access for pertussis vaccination in New Zealand was a 3-component aP vaccine recommended at the following times in children aged 6 weeks, 3 months, 5 months, (as part of DTa-IPV-HepB/Hib), 4 years (DTaP-IPV) and 11 years (Tdap). Members also noted that a 3-component aP vaccine was funded for pregnant women 28 to 38 week's gestation during epidemics.
- 4.6 The Committee noted the Environmental Science and Research (ESR) July-September 2013 surveillance report on pertussis. Members noted that since 1 August 2011, when the current pertussis epidemic began, through to 6 September 2013, there were a total of 10,311 pertussis cases (confirmed, probable and suspected), 580 hospitalisations and three notified deaths. Of these deaths, two were too young to have started their immunisation programme and one was an unvaccinated child. From 21 September to 4 October 2013, 89 new cases were reported.
- 4.7 The Committee noted that infants (under one year old) are the population at highest risk of serious outcomes and since the start of the outbreak have accounted for 730

cases (7%) and 339 of all hospitalisations (58%). Māori and Pacific children <1 year are significantly more likely to be hospitalised with pertussis.

- 4.8 The Committee noted the Cochrane review Zhang et al 2012: Acellular vaccines for preventing whooping cough in children. Six efficacy trials with a total of 46,283 participants. Five studies published between 1995 and 1998. The trials included double-blind randomised controlled trials (RCT) with active follow up of participants (children <6 years) and laboratory verification of pertussis cases. The studies used the World Health Organization (WHO) definition of typical whooping cough >21 days of paroxysmal cough with culture or serology confirmed *Bordetella pertussis* infection or contact with a household member with confirmed pertussis infection whilst mild disease was defined as >7 days of paroxysmal cough with confirmed pertussis infection. Efficacy of 3 or more component vaccine varied from 84-85% in preventing typical whooping cough and 71-78% in preventing mild disease (Greco 1996; Gustafsson 1996). By contrast the efficacy of 1- and 2-component vaccines varied from 59%-78% against typical whooping cough and 41-54% against mild whooping cough (AHGSPV 1988 review, Trollfors 1995). It was recognised that the 2-component vaccines evaluated in these studies were different from the 2-component vaccine being considered by PHARMAC.
- 4.9 The Committee noted the AHGSPV (1988 Lancet) Study. The Committee noted the Swedish double blind parallel group RCT. Subjects received either 2 doses of 1- or 2-component aP vaccine or placebo. 2837 randomised to receive aP and 954 placebo. Subjects were followed for 17-19 months after the second of 2 vaccinations. The vaccine efficacy of 78% (CI 58-89) for whooping cough for the 2-component vaccine and 58% (35-73) for mild pertussis.
- 4.10 The Committee noted the Gustafsson et al study (NEJM 1996). Swedish double blind parallel group RCT, subjects received 3 doses of 2-component, 5- component aP vaccine, whole cell Pertussis vaccine or placebo (Diphtheria Tetanus vaccine). 9829 infants randomised, of whom 2566 received 2-component aP vaccine and were followed for 21 months. Vaccine efficacy of 59% (CI 51-66) for whooping cough for the 2-component vaccine and 44% (35-52) for mild pertussis.
- 4.11 The Committee noted a systematic review by Jefferson et al (Vaccine 2003) which included cohort studies as well as RCTs concluded that 1- and 2- component aP vaccines have significantly lower vaccine efficacy than 3- or more component aP vaccines. The authors comment that RCTs measure vaccine efficacy but not effectiveness of a large scale vaccination programme which may have reduced compliance and “real-world” difficulties.
- 4.12 The Committee noted the Plotkin et al 2011 review of the 2-component aP vaccine in Pentaxim (Sanofi-Pasteur) which showed that there were high seroconversion rates for both anti-PT and anti-FHA antibody titres.
- 4.13 The Committee noted that some counties in Sweden have used the 2-component aP vaccine and others the 3-component vaccine, and since the use of the different vaccines has varied with and within calendar periods and areas, no long term head-to-head comparisons have been published.
- 4.14 The Committee noted that Japan was the first country to introduce aP vaccination and has considerable experience and safety data. Members noted that high quality efficacy data for the 2-component vaccine in Japan is lacking with early household studies having significant methodological flaws. Members noted that the changes to the vaccination schedule for pertussis in Japan were summarized in Kuno-Sakai

(Pediatr Int. 2004). The review details the history of introduction of 1- and 2-component aP vaccine in Japan with the first dose at age 2 years due to concerns of encephalopathy occurring in younger infants. In 1989 the age of first dose was changed to 3 months with corresponding marked reduction in cases. Members noted the reporting system was as cases/ doctor/ year, which made the data difficult to interpret.

- 4.15 Members noted that the WHO recommends a 3- or more component aP vaccine, based on the recommendations of the Jefferson (2003) review and the Cochrane review.
- 4.16 The Committee noted that a 2-component vaccine has good seroconversion data and experience in Sweden, Denmark and Japan, which suggested that less than 3-component aP vaccines are effective as part of national vaccination programmes in controlling pertussis. The Committee noted that there was emerging data from France and Germany on the use of 2-component pertussis vaccinations.
- 4.17 The Committee noted that the differences in society between New Zealand and these countries however may be important to consider. Members noted that Denmark and Sweden have for many years had >95% vaccination rates in infancy, low levels of child poverty (overcrowding, access to health care) as determined by UNICEF. Importantly, not only do these countries have near 100% vaccination rates, but the vaccines are given on time.
- 4.18 Members noted that New Zealand is currently experiencing a pertussis epidemic. Members consider that there could be risks in changing from a 3- component vaccine to a 2-component vaccine without higher, and more timely immunisation rates in children. Members noted that this would particularly apply to Māori who have the highest rates of severe pertussis infection in infancy, and the lowest rates of vaccination at 6 months of age.
- 4.19 The Committee **recommended** that PHARMAC seek the advice of the Immunisation Subcommittee as to the appropriateness of the current pertussis vaccination schedule, including whether an additional dose at 12-15 months would be appropriate. The Committee requested advice from the Immunisation Subcommittee on whether a 2-component aP vaccine would be acceptable for funding on the Immunisation Schedule.
- 4.20 The Committee **recommended** that due to the current rate of vaccination being less than 95% and that patients were not receiving vaccination at the recommended time that PHARMAC not change to a 2-component aP vaccination on the Immunisation Schedule at this time.

5 Ciprofloxacin

Application

The Committee considered an application from the New Zealand Society of Otolaryngology Head and Neck Surgery for the funding of ciprofloxacin eye drops (for aural use) for chronic suppurative otitis media (extending the subsidy for ciprofloxacin eye drops for use in the middle ear).

Recommendation

- 5.1 The Committee **recommended** removal of the wording that ciprofloxacin eye preparations “are only funded for use in the eye, unless explicitly stated otherwise” to “are funded for second line treatment of bacterial infections” with a high priority.
- 5.2 The Decision Criteria particularly relevant to these recommendations are: *(ii) The particular health needs of Māori & 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 & disability support services; (vii) The Government’s priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC’s Funding Agreement, or elsewhere.*

Discussion

- 5.3 The Committee noted that the New Zealand Society of Otolaryngology Head and Neck Surgery has requested that PHARMAC considers extending the subsidy for ciprofloxacin eye drops for use in the middle ear.
- 5.4 The Committee noted that chronic suppurative otitis media (CSOM) is a persistent infection of the middle ear, accompanied by a perforated tympanic membrane. The Committee noted that most of the responsible bacteria are those common to the external auditory canal, (i.e present in the externa but infecting the media); *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Proteus* species, *Klebsiella pneumoniae*, and diphtheroids. Anaerobic bacteria and fungi may grow concurrently with the aerobic bacteria.
- 5.5 The Committee noted that the following ear drops and eye/ear drops are listed in on the Pharmaceutical Schedule:
- Chloramphenicol Eardrops 0.5%
 - Flumetasone Pivalate 0.02% with clioquinol 1%.
 - Triamcinolone acetoneide with gramicidin, neomycin and nystatin
 - Dexamethasone with framycetin and gramicidin
 - Framycetin Sulphate
- 5.6 The Committee noted that the majority of the listed products contain aminoglycosides. Members noted that all funded ear and eye/ears drops have specific contraindications in the setting of CSOM where there is a known perforation of the tympanic membrane. The data sheet for the non-funded, but registered, otic preparations (Ciproxin HC) states that it is not indicated in known or suspected tympanic perforation. The otic preparation, Cilodex has an indication for acute otitis media with tympanostomy tubes but does not talk about CSOM. A member noted that the issue that ophthalmic drops do not have a listed indication in the datasheet for acute or chronic otitis media with tube or perforation. Neither of the otic preparations is subsidised in the community schedule and the eye preparation has a specific listing for eyes only.
- 5.7 The Committee noted the importance and relevance of CSOM in New Zealand. Some older studies show rural Māori children have a very high rate of CSOM (Giles NZ Med J. 1989 12;102(865);160-1. Giles et al J Laryngol Otol. 1991;105(4):257-60;

Giles et al Clin Otolaryngol Allied Sci.1991;16(2):174-8). The Committee noted a more recent New Zealand study which reported 3871 hospital admissions for otitis media per 100 000 of the population of children under five years of age, with higher rates of medical admissions amongst Māori and Pacific children (Fireman et al Pediatr Infect Dis J. 2003 22(1):10-6.).

- 5.8 The Committee noted a review by Macfadyen et al (Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD005608) of systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations. The review included nine trials (833 randomised participants; 842 analysed participants or ears). Topical quinolone antibiotics were better than systemic antibiotics at clearing discharge after between one and two weeks of treatment: 1-2 weeks: relative risks (RR) were, 3.21 (95% confidence interval (CI) 1.88 to 5.49) compared with using systemic non-quinolone antibiotics (2 trials, N = 116), and 3.18 (1.87 to 5.43) compared with using systemic quinolone (3 trials, N = 175); or 2.75 (1.38 to 5.46). These results favour systemic plus topical quinolone over systemic quinolone alone (2 trials, N = 90). No statistically significant benefit was seen at 2-4 weeks for topical non-quinolone antibiotic (without steroids) or topical antiseptic over systemic antibiotics (mostly non-quinolones), but numbers were small: one trial tested topical non-quinolones (N = 31); two tested antiseptics (N = 152). No benefit of adding systemic to topical treatment at 1-2 weeks was detected either, although evidence was limited (three trials, N = 204). The Committee noted that the evidence regarding safety was generally weak. Members noted that adverse events reported were generally mild, although hearing worsened by ototoxicity (damaging auditory hair cells) was seen with chloramphenicol drops (non-quinolone antibiotic).
- 5.9 The Committee noted that there was a difference in the consensus view between the United States and the UK. Members noted that due to the concern for ototoxicity with aminoglycoside containing agents, the 2004 American Academy of Otolaryngology-Head and Neck Surgery consensus panel recommended that "When possible, topical antibiotic preparations free of potential ototoxicity are preferred over otological agents that have the potential for injury if the middle ear and mastoid are open" (Roland et al. Otolaryngol Head Neck Surg 2004; 130:S51, Matz et al Otolaryngol Head Neck Surg 2004; 130:S79). The Committee noted the UK view on the use of aminoglycoside-containing ear drops was published 2007 by the British Association of Otolaryngologists (Phillips et al Clin Otolaryngology 2007;32:330-6) 2007) emphasised the lack of well-designed clinical trials concerning ototoxicity from ear drops; animal studies and case reports making up the majority of available data. Members noted that a consensus survey completed by otolaryngologists in the UK recommended use of aminoglycoside ear drops only in cases with documented infection, and for a maximum of two weeks. The Committee noted that ENT-UK recommends that when treating a patient with a discharging ear, in whom there is a perforation or patent grommet that if a topical aminoglycoside is used it should only be in the presence of obvious infection. Members noted that ENT-UK also recommended topical aminoglycosides should be used for no longer than 2 weeks.
- 5.10 Members noted the severity of complications of CSOM including mastoiditis and that sequelae include hearing loss and tympanosclerosis.
- 5.11 The Committee noted a recent publication by Winterstein et al (Otolaryngology-Head and Neck Surgery. 2013:148;277-283). The authors undertook an administrative claims analysis in children receiving ear drops for non-intact tympanic membranes and found that 983 sensorineural hearing loss (SNHL) cases

in 134,598 children treated with neomycin or fluroquinolones. Members noted that the authors concluded that short term use of neomycin was not associated with increased risk of SNHL, but that repeated courses showed an increased risk of SNHL.

- 5.12 The Committee considered that quinolone ear drops are either more effective or at least equivalent to existing (aminoglycoside) ear drops for CSOM. The Committee considered that the evidence of actual toxicity from existing (non-quinolone) preparations to be weak but that theoretical and animal studies suggest a higher potential for ototoxicity. Members noted that the increased toxicity rate with aminoglycosides would be in the region of 2-3 per 1000 treated children. Next few paragraphs may need to be combined I have done a bit
- 5.13 In general the committee did not support aural usage of preparations not formulated for the ear but given the toxicity of existing compounds and lack of alternatives considered that ciproxin eye drops (for the ear) should be restricted to children with tympanotomy tubes.
- 5.14 The Committee considered that the microbiological/ ecological impact of use of topical quinolones in eye and ear infections is complex and should be referred to the Anti-Infective Subcommittee for comment.
- 5.15 Members considered that changing the special authority criteria for the use of ophthalmic drops to include the statement for second line treatment of bacterial infection may lead to extensive prescribing in otitis externa.
- 5.16 Members noted that the data sheet for ciprofloxacin eye drops does not list an indication for ear use and that the use of this agent would be outside its registered indication.
- 5.17 The Committee noted that since the eye drops are not registered for otic use they would need to be prescribed under section 25 of the Medicine Act if used aurally.

6 Axitinib for second line treatment of metastatic clear cell renal cancer

Application

The Committee reviewed an application from Pfizer (NZ) Ltd for the funding of axitinib (Inlyta) on the Pharmaceutical Schedule as for patients with metastatic clear cell renal cell carcinoma (mRCC) where disease progression or intolerance has occurred following prior tyrosine kinase inhibitor treatment.

Recommendation

- 6.1 The Committee **recommended** that the application for axitinib be declined.

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

Discussion

- 6.3 The Committee noted that axitinib was a new oral tyrosine kinase inhibitor (TKI) indicated for the treatment of patients with advanced renal cell carcinoma after failure of one prior systemic therapy. Members noted that the application was for patients who had failed currently funded first line TKI treatments pazopanib or sunitinib. The Committee noted that it had previously recommended that an application for the funding of everolimus, an mTOR inhibitor, for the same population as being requested in this application, be declined.
- 6.4 The Committee noted that currently funded first line treatment options for patients with mRCC included interferon alpha and the TKIs sunitinib and pazopanib. Members considered that there was an unmet health need in patients with disease refractory to sunitinib or pazopanib, with treatment options in this setting limited to interferon or more likely best supportive care.
- 6.5 The Committee noted key evidence provided in the application comprised a phase III study comparing axitinib with sorafenib (A4061032 AXIS study) and a sub-analysis of patients receiving sorafenib or best supportive care from a retrospective non-interventional study from Sweden (RENCOMP) to support indirect comparison of axitinib with best supportive care. Members noted there was no direct evidence comparing axitinib with relevant comparators in NZ, namely, interferon or best supportive care.
- 6.6 The Committee noted that the AXIS study (*Rini B. Lancet. 2011; 378 (9807): 1931-1939 and Motzer RJ et al. Lancet Oncology, 2013;14:552-562*) was a phase III, randomised, open-label study of comparing axitinib with sorafenib in 723 patients with mRCC progressing after first line treatment. Members noted that patients were randomised in a 1:1 ratio to receive axitinib (n=366), at a starting dose of 5mg twice daily (with the option of dose titration to a maximum of 10 mg twice daily), or sorafenib (n=362), at a dose of 400mg twice daily.
- 6.7 The Committee noted that 54% of the patients enrolled had received prior sunitinib treatment, the remainder cytokines (35%), bevacizumab (8%) or temsirolimus (3%). Members further noted that the mean total daily dose in the axitinib treated patients was 10.6 mg and mean days of treatment was 221 (range 1-670) compared with 180.7 for sorafenib. Members noted that crossover between study drugs was not allowed, however, treatment with further systemic therapy was permitted - of the patients who discontinued treatment 28% (101) of patients in the axitinib arm and 37% (133) of patients in the sorafenib arm received follow-up systemic therapy.
- 6.8 The Committee noted that the primary endpoint of the study, median progression free survival (PFS) as determined by independent radiological review, was 6.7 months for axitinib and 4.7 months for sorafenib (HR 0.665 (95% CI: 0.544, 0.812) p = <0.0001), a 2 month difference. Members further noted that in a subgroup analysis of the patients who had received prior sunitinib median PFS for axitinib

was 4.8 months and sorafenib was 3.4 months (HR 0.741 (95% CI: 0.573, 0.958) p =0.0107), a 1.4 month difference. Median Overall Survival (OS) for the axitinib arm was 20.1 months compared with 19.2 months for the sorafenib arm in patients who had received prior sunitinib median OS for the axitinib arm was shorter at 15.2 months compared with 16.5 months for the sorafenib arm. Neither OS result reached statistical significance.

- 6.9 The Committee considered that overall there was moderate strength and quality of evidence for improved PFS with axitinib treatment compared with sorafenib in the second line mRCC setting but no good evidence that axitinib improves overall survival or quality of life compared with sorafenib.
- 6.10 The Committee noted that in lieu of direct evidence comparing axitinib with best supportive care the supplier provided a subanalysis of patients receiving sorafenib in the RENal COMParison (RENCOMP) study, which was a retrospective, non-interventional study using data from a Swedish Cancer Register and two other national registries, in the form of an unpublished poster (Sandstrom et al ESMO, Austria, Sept-Oct, 2012. Poster 848P). Members noted that in 135 patients receiving sunitinib first line followed by sorafenib OS for was 9.2 months, compared with 5.4 months for best supportive care. Members also noted evidence from four other, abstract only, retrospective studies of survival after first line TKI failure which provided OS estimates that ranged from 4.1 to 6.97 months.
- 6.11 The Committee noted that based on an indirect comparison of axitinib with best supportive care (BSC), using results of the sunitinib pre-treated subgroup from AXIS and the retrospective unpublished analyses of sorafenib vs. BSC the supplier considers that axitinib is likely to offer similar advantages to sorafenib over best supportive care in the second line setting. Members noted the supplier estimated an overall survival gain of 3.7 months for axitinib compared with BSC (15.2 months axitinib vs. 11.5 months BSC). The committee considered that because it was based on indirect comparisons, retrospective sub analyses, and observational studies the evidence to support the assumption of benefit for axitinib over best supportive care was very weak, subject to a high risk of bias and had a large margin of uncertainty around any estimate.
- 6.12 The Committee noted evidence from a recent publication comparing first line treatment with pazopanib vs. sunitinib (*Motzer et al N Engl J Med 2013; 369:722-731*) which suggested around 20 month's survival post progression, therefore, members considered that treatment length for axitinib would be more likely 20 months compared with 15-17 for BSC.
- 6.13 The Committee considered that overall the evidence base for axitinib in the population being requested for funding was weak and it would likely be associated with very high cost. Members considered that other new treatments likely to be available in the near future might offer better evidence for benefit. Members considered that strength of evidence supporting the use of axitinib did not justify its very high cost.

7 **Zoledronic acid for hypercalcaemia of malignancy, treatment of pain in bone metastases and prevention of skeletal related events in patients with bone metastases**

Application

The Committee reviewed an application from PHARMAC staff for the funding of zoledronic acid (4 mg in 5 ml) in hospitals and in the community for treatment of hypercalcaemia of malignancy, treatment of pain in patients with bone metastases and prevention of skeletal-related events (SRE) in patients with bone metastases.

Recommendation

- 7.1 The Committee **recommended** that zoledronic acid (4 mg in 5 ml) should be funded in hospital and in the Community subject to Special Authority criteria for the treatment of hypercalcaemia of malignancy, treatment of pain in patients with bone metastases and prevention of skeletal-related events (SRE) in patients with bone metastases if cost neutral to pamidronate taking into account the costs of infusion services and compounding.
- 7.2 The Committee **recommended** that in the Community Special Authority applications should be limited to Palliative Care Specialists or Oncologists.
- 7.3 The Decision Criteria particularly relevant to this recommendation are *ii) The particular health needs of Māori & Pacific peoples; (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 Schedule; (vii) The direct cost to health service users.*

Discussion

- 7.4 The Committee noted that zoledronic acid 4 mg in 5 ml (Zometa) is currently listed on the HML, restricted to the treatment of hypercalcaemia of malignancy, and is not listed in Section B of the Pharmaceutical Schedule. Members noted that PHARMAC had received requests to widen HML access for zoledronic acid (4 mg in 5 ml) to include prevention of skeletal related events (SREs) in patients with bone metastases (including in the absence of hypercalcaemia) and to list this formulation of zoledronic acid in Section B of the Pharmaceutical Schedule for the same indications.
- 7.5 The Committee noted that PHARMAC sought the advice of the Analgesic Subcommittee at its 24 September 2013 meeting where it considered that as well as the indications listed above zoledronic acid may be useful for the reduction of pain in patients with bone metastases (in the absence of fractures and hypercalcaemia). The Subcommittee noted that it had not had the opportunity to review all the relevant studies – of which there were many, including several meta-analyses – and recommended that a full review should be conducted by PTAC and/or the Cancer Treatments Subcommittee of PTAC.
- 7.6 The Committee noted that an alternative bisphosphonate, pamidronate, was fully funded in both Hospitals and the Community without restriction but that uptake of this drug was limited, especially in the Community, and considered that this was probably because it required infusion over 90 minutes.
- 7.7 The Committee considered a large amount of evidence from many primary and secondary sources including several Cochrane reviews on the use of zoledronic acid in the various settings outlined above in patients with various underlying malignancies, mainly breast and prostate cancer and multiple myeloma. Members considered evidence, where available, for the use of bisphosphonates in general, the use of zoledronic acid versus placebo/usual care and the use of zoledronic acid versus other bisphosphonates including pamidronate.
- 7.8 The Committee considered that the strength and quality of the evidence was highly variable depending on the setting and question being addressed. For example there was high quality and good strength of evidence for benefit for bisphosphonates compared with placebo/control for SRE and pain but weak strength for hypercalcaemia in myeloma compared with high quality and good strength for SRE but no evidence for pain or hypercalcaemia in breast cancer.
- 7.9 The Committee considered that given the paucity of evidence in some settings, and the variable quality and reporting of evidence where it was available, it was highly likely that the evidence was confounded by significant publication selection bias.

- 7.10 The Committee considered that overall there was sufficient evidence to conclude that bisphosphonates treatment was beneficial in all 3 indications compared with no bisphosphonate treatment. However, members considered that there was no evidence for any additional health benefit of zoledronic acid over other bisphosphonates currently available in New Zealand, in particular pamidronate. Members noted that zoledronic acid may be associated with increased incidence of osteonecrosis of the jaw compared with pamidronate.
- 7.11 The Committee considered that the shorter infusion time of zoledronic acid (15 minutes) compared with pamidronate (90 minutes) may be beneficial to DHB hospitals and more convenient for patients however, members considered that nursing time for IV preparation and set up would be similar between the two treatments with just physical occupation of bed time being the main difference. However, members considered that shorter bed stays would result in more capacity being created for more patients to be treated within the available service.
- 7.12 The Committee considered that if access to zoledronic acid was widened in hospitals most patients currently receiving pamidronate would instead receive zoledronic acid. Members also considered that the market would grow since it was possible that infusion constraints were currently limiting access to pamidronate in hospitals.
- 7.13 The Committee considered that access to zoledronic acid should be the same in the community as it is in hospitals noting that hospices and some PHOs may offer IV infusion services albeit at the expense of patients. Members considered it likely that access in the community would grow the market but that it was sensible for access in the community to match that of the hospitals to avoid confusion and so that it could be administered in the community if possible. Members considered that zoledronic acid treatment in the community should only be initiated by a palliative care specialist or an oncologist.
- 7.14 The Committee noted that price of zoledronic acid 4 mg in 5ml had reduced recently and would likely reduce further due to generic competition; therefore the long term fiscal risk of widening access in hospitals and listing in the community would likely be low.

8 Tocilizumab for rheumatoid arthritis

Application

The Committee reviewed a submission from Roche Products (NZ) Ltd for the funding of tocilizumab (Actemra) on the Pharmaceutical Schedule as a first-line biologic treatment for patients with rheumatoid arthritis who cannot take methotrexate.

Recommendation

- 8.1 The Subcommittee **recommended** that access to tocilizumab on the hospital medicines list (HML) be widened to include treatment of rheumatoid arthritis as monotherapy in patients who cannot take methotrexate, subject to the following restrictions, with a low priority:

Initiation —Rheumatoid Arthritis - rheumatologist

Re-assessment required after 6 months

All of the following:

- 1 Patient has had severe and active erosive rheumatoid arthritis for six months duration or longer; and
- 2 Tocilizumab is to be used as monotherapy; and
- 3 Either:
 - 3.1 Treatment with methotrexate is contraindicated; or
 - 3.2 Patient has tried and did not tolerate oral and parenteral methotrexate; and
- 4 Either:
 - 4.1 Patient has tried and not responded to at least three months therapy at the maximum tolerated dose of cyclosporine alone or in combination with another agent; or
 - 4.2 Patient has tried and not responded to at least three months therapy at the maximum tolerated dose of leflunomide alone or in combination with another agent; and
- 5 Either:
 - 5.1 Patient has persistent symptoms of poorly controlled and active disease in at least 20 active, swollen, tender joints; or
 - 5.2 Patient has persistent symptoms of poorly controlled and active disease in at least four active joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip; and
- 6 Either:
 - 6.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or
 - 6.2 C-reactive protein levels not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months.

Continuation – rheumatologist or practitioner on recommendation of a rheumatologist

Re-assessment required after 6 months

Either:

- 1 Following 6 months initial treatment, the patient has at least a 50% decrease in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician; or
- 2 On subsequent reapplications, the patient demonstrates at least a continuing 30% improvement in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician.

- 8.2 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; and,(iv)The clinical benefits and risks of pharmaceuticals;

Discussion

- 8.3 The Committee noted that it had reviewed an application from Roche to list tocilizumab on the HML for rheumatoid arthritis and systemic juvenile idiopathic arthritis (sJIA) at its meeting in November 2011 and that application had also been

reviewed by the Rheumatology Subcommittee of PTAC at its October 2011 meeting.

- 8.4 The Committee noted that in November 2011 it had recommended that tocilizumab be listed on the HML for patients with sJIA who have not responded to prior treatment with NSAIDs, methotrexate and systemic corticosteroids, with a high priority, and that this had been implemented from 1 July 2013.
- 8.5 The Committee noted that it had recommended that tocilizumab be listed on the HML for patients with rheumatoid arthritis who have not responded to prior treatment with standard disease-modifying anti-rheumatic agents (DMARDs) and at least one tumour necrosis factor (TNF) inhibitor, with a low priority, which had not been progressed by PHARMAC.
- 8.6 The Committee noted that Roche had submitted a response to the November 2011 PTAC minutes, including longer-term safety and efficacy data and an application (including a commercial proposal) to list tocilizumab on the HML for use as a first-line biologic treatment option, as monotherapy, in patients with rheumatoid arthritis who cannot use methotrexate.
- 8.7 The Committee noted that rituximab, adalimumab, etanercept and infliximab are currently listed on the HML for the treatment of rheumatoid arthritis, and that adalimumab and etanercept are also listed in Section B of the Pharmaceutical Schedule for the treatment of rheumatoid arthritis.

Longer-term safety and efficacy data

- 8.8 The Committee noted that the supplier had provided unpublished reports (Jones et al. ACR Annual Scientific Meeting November 2012; abstract & poster #454) on a post-hoc exploratory analysis of 243 patients who entered a long-term extension of the AMBITION study (a 24-week, randomised controlled trial of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate-to-severe rheumatoid arthritis). Patients in the extension study were treated with tocilizumab 8 mg/kg monotherapy for up to 240 weeks; DMARDs (including methotrexate) could be added per investigator discretion in patients who did not experience a 50% reduction in tender and swollen joints from baseline of the core study. A total of 139 patients remained on tocilizumab until withdrawal or data cutoff. The Committee noted that DAS28 levels were maintained up to 240 weeks of follow-up, although it appeared that over time an increasing number of patients required additional DMARDs to maintain efficacy. The Committee noted that adverse effects appeared to remain stable over time.
- 8.9 The Committee noted that the supplier had also provided published and unpublished reports of pooled safety data from long-term studies (Genovese et al. ACR Annual Scientific Meeting November 2012; abstract #1640; Nishimoto et al, Mod Rheumatol 2010;20:222-32). The Committee considered that these reports suggested that the serious adverse event rates remain relatively stable over time at around 19 to 23 per 100 patient years, with approximately one quarter of these being serious infections. The Committee considered that the reports did not appear to raise any new safety concerns.

Tocilizumab monotherapy

- 8.10 The Committee noted a phase 4 randomised, double-blind controlled-phase trial of tocilizumab monotherapy versus adalimumab monotherapy in patients with severe rheumatoid arthritis who had previously used methotrexate and in whom methotrexate was not tolerated or the investigator considered methotrexate was not appropriate for continued use (the ADACTA trial, Gabay et al. *Lancet* 2013;381(9877):1541-50). The primary efficacy measure was the change in disease activity score using 28 joints (DAS28) from baseline to week 24, with secondary endpoints including American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) response rates.
- 8.11 The Committee noted that there was a statistically significant difference in the mean change of DAS28 from baseline to week 24 between the two groups (-3.3 for tocilizumab and -1.8 for adalimumab, difference of -1.5, 95% CI -1.8 to -1.1; $p < 0.0001$), and that response rates were significantly higher for tocilizumab for all secondary endpoints.
- 8.12 The Committee considered that the study was associated with a number of potentially limiting factors, including a lack of explanation for why nearly 30% of the screened patients were considered ineligible to be enrolled; the relatively low adalimumab response rates compared with what might have been expected from previous adalimumab trials; and the fact that more than 60% of patients continued methotrexate until within 2 months of study baseline, suggesting that these patients were not truly intolerant of methotrexate and, therefore, may not be representative of the target population in New Zealand.
- 8.13 The Committee noted that a similar number of patients in each treatment arm withdrew early from ADACTA and that adverse events and infection rates were similar between groups, although more patients treated with tocilizumab have raised alanine aminotransferase (ALT) concentration, raised low-density lipoprotein, and reduced neutrophil and platelet counts. More patients in the tocilizumab arm required dose modification or interruption because of adverse events.
- 8.14 The Committee noted the publication of ACT-STAR (Weinblatt et al. *Arthritis Care Res.* 2013;65:362-371), an open-label study in 886 patients designed to reflect clinical practice to test safety and tolerability of tocilizumab as monotherapy or in combination with DMARDs in patients with moderate to severe active rheumatoid arthritis who had inadequate response to therapy at study entry, and to explore the effect of increasing tocilizumab dosing from 4 mg/kg to 8 mg/kg. Patients on biologic monotherapy at study entry were assigned to tocilizumab 8 mg/kg monotherapy and all other patients were assigned to tocilizumab 4mg/kg plus DMARDs or tocilizumab 8mg/kg plus DMARDs. The primary end point was number and percentage of patients with serious adverse events at 24 weeks; all efficacy endpoints were secondary, including ACR 20, 50 and 70 and DAS assessments.
- 8.15 The Committee noted that the overall serious adverse event rate per 100 person-years in ACT-STAR was 28.3 (95% CI 23.1-34.4), which was similar across treatment groups. Gastrointestinal perforation occurred in three patients and there were two deaths during the study period, one of which was thought to be due to study medication. Approximately 28% of patients had raised ALT levels at 24 weeks, the majority of which low-grade elevations. A total of 25.8% (58) of patients with raised ALT discontinued tocilizumab after the worst occurrence. Grade 3 neutropenia occurred in 19 patients, 16 of whom were on higher doses of tocilizumab. Low platelet count occurred in 12%-15% in all groups but no severe

thrombocytopenia was noted. Efficacy outcomes were similar between the groups. ACR20 and ACR 50 responses were noted in approximately 42%-49% and 21%-23%, respectively, of patients after 24 weeks in all groups.

- 8.16 The Committee noted that the ACT-STAR study had some limitations including the open-label design and uneven matching of clinical features between treatment groups at baseline; however, the Committee considered that it provided a useful insight into clinical experience using tocilizumab. The Committee noted that, overall, the serious adverse event rate in ACT-STAR appeared to be higher than in the randomised clinical trials while the efficacy rate appeared lower.
- 8.17 The Committee noted that the 24-weeks results of ACT-RAY have now been published (Dougados et al, *Ann Rheum Dis* 2013;72:43-50) and that the supplier had provided the unpublished 52-week results in abstract form. ACT-RAY was a double-blind, 2-year study in which 552 adults with active rheumatoid arthritis on stable doses of methotrexate were randomised to either add tocilizumab 8 mg/kg every four weeks to their existing methotrexate or switch to tocilizumab 8 mg/kg with oral placebo. Open-label DMARDs other than methotrexate were added at week 24 or later. The primary endpoint was the DAS28-erythrocyte sedimentation rate (ESR) remission rate at week 24. A total of 85% of patients completed 52 weeks of treatment. At week 24, DAS28-ESR remission rates were 40.4% for tocilizumab plus methotrexate and 34.8% for tocilizumab plus placebo (p=0.19); these results were maintained or improved between 24 and 52 weeks. At 52 weeks, the rates of serious adverse events and serious infections per 100 patient-years were 14.2 and 4.9 for tocilizumab plus methotrexate and 17.7 and 6.3 for tocilizumab plus placebo, respectively. The Committee noted that approximately a third of patients in both groups required DMARD intensification between weeks 24 and 52.
- 8.18 The Committee considered that the available evidence for tocilizumab monotherapy was of reasonable quality and strength and suggested that tocilizumab monotherapy would likely provide slightly reduced efficacy when compared to tocilizumab with methotrexate and slightly improved efficacy when compared to adalimumab monotherapy in a real world setting. The Committee noted that over time patients on tocilizumab monotherapy appeared to require additional DMARDs to maintain therapeutic benefit, and a large proportion (up to one-third) of patients appeared to discontinue tocilizumab.
- 8.19 The Committee noted that the supplier had estimated that approximately 18% of patients eligible for biologic treatment in New Zealand would be considered unable to take methotrexate due to intolerance. However, the Committee noted that PHARMAC's data show that approximately one-third of patients on adalimumab or etanercept use these treatments without methotrexate, and the Committee considered that this figure was probably closer to the proportion of patients likely to take biologics without methotrexate in New Zealand.
- 8.20 The Committee noted the draft minute from the Rheumatology Subcommittee of PTAC's October 2013 meeting during which the submission from Roche had been discussed. The Committee noted and agreed with the Subcommittee's view that patients who couldn't take methotrexate could take a biologic treatment with leflunomide or other DMARDs – i.e. monotherapy with a funded biologic agent was not the only treatment option for these patients.
- 8.21 The Committee disagreed with the Subcommittee's view that tocilizumab would be unlikely to significantly grow the biologics market if it were available as requested by

the supplier; the Committee considered that it would both grow the biologics market and extend the duration of biologic treatment.

- 8.22 The Committee considered that the criterion relating to methotrexate intolerance in the restrictions proposed by the supplier – that the patient has tried and did not tolerate oral or parenteral methotrexate – was too permissive, in that it was reasonably common for patients to tolerate parental methotrexate who were previously intolerant to oral methotrexate. Therefore, the Committee considered that the criterion should require intolerance to parental methotrexate.
- 8.23 The Committee considered that most patients would probably prefer to self-inject a community funded tumour necrosis factor (TNF) inhibitor rather than receive a 4-weekly intravenous infusion in hospital, all other factors being equal; however, the Committee considered that this would be unlikely to influence use of the TNF inhibitors versus tocilizumab in the longer term if clinicians considered that tocilizumab was more effective than TNF inhibitors as monotherapy in patients who cannot take methotrexate. Members noted that there is a subcutaneous presentation of tocilizumab in development.
- 8.24 The Committee considered that PHARMAC staff's adjustments to the supplier's estimate of the yearly cost of tocilizumab (i.e. to include potential wastage and infusion costs) were reasonable.

9 Adalimumab for weekly dose rescue therapy for Crohn's disease

Application

The Committee considered a request from a clinician for the funding of a weekly dosing regimen for adalimumab for Crohn's disease for patients who do not receive a sustained response from fortnightly dosing.

Recommendations

- 9.1 The Committee recommended that adalimumab be listed in the Pharmaceutical Schedule with a low priority, subject to Special Authority criteria:
- 9.1.1 The Committee recommended that funding should be restricted to one short course of up to six 40mg doses per annum and recommended referral to the Gastro-Intestinal Subcommittee for further advice relating to the details of the Special Authority criteria.
- 9.2 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; (ix) Such other criteria as PHARMAC thinks fit.

Discussion

- 9.3 The Committee noted that adalimumab is currently funded for the treatment of rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, fistulising Crohn's disease, severe chronic plaque psoriasis and psoriatic arthritis. Members noted that following the widening of access to adalimumab in 2009 for Crohn's disease, PHARMAC has received an enquiry from a clinician asking if the funding rules could be widened to permit weekly dosing of adalimumab for Crohn's disease for patients who have not received a sustained response from fortnightly dosing of adalimumab.
- 9.4 The Committee noted that PHARMAC had sought its advice in February 2010 regarding whether weekly dosing should be excluded from the funded renewal access criteria for adalimumab for Crohn's disease. At this time, the Committee recommended that 40 mg weekly dosing be specifically excluded from the adalimumab renewal criteria.
- 9.5 The Committee noted that PHARMAC had sought its further advice on the Special Authority criteria for adalimumab in November 2011 and that the Committee recommended that no changes be made either to the current initial or renewal Special Authority criteria for adalimumab for Crohn's disease.
- 9.6 The Committee noted that in its Therapeutic Group Review in April 2012, the Gastroenterology Subcommittee of PTAC had recommended that PHARMAC staff re-model previous cost-effectiveness estimates for this therapy and for 'rescue therapy' to be reconsidered for funding.
- 9.7 The Committee noted a [previously considered] study by Colombel et al (*Gastroenterology*. 2007 Jan;132(1):52-65). (The CHARM study.) Patients received open-label induction therapy with adalimumab 80 mg (week 0) followed by 40 mg (week 2). At week 4, patients were stratified by response (decrease in Crohn's Disease Activity Index > or =70 points from baseline) and randomised to double-blind treatment with placebo, adalimumab 40 mg every other week, or adalimumab 40 mg weekly through week 56. Co-primary end points were the percentages of randomised responders who achieved clinical remission (Crohn's Disease Activity Index score <150) at weeks 26 and 56. The percentage of randomised responders in remission was significantly greater in the adalimumab 40-mg every other week and 40-mg weekly groups versus placebo at week 26 (40%, 47%, and 17%, respectively; $P < .001$) and week 56 (36%, 41%, and 12%, respectively; $P < .001$). Members noted that no significant differences in efficacy between adalimumab every other week and weekly were observed.
- 9.8 The Committee noted a [previously considered] study by Sandborn et al (*Gut*. 2007 Sep;56(9):1232-9.) (CLASSIC II) which evaluated long term efficacy and safety of adalimumab maintenance therapy in Crohn's disease in a follow-on randomised controlled trial. In the preceding CLASSIC I trial, 299 patients with moderate to severe Crohn's disease naive to tumour necrosis factor antagonists received induction therapy with adalimumab 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg, or placebo, at weeks 0 and 2. In all, 276 patients from CLASSIC I enrolled in CLASSIC II and received open-label adalimumab 40 mg at weeks 0 (week 4 of CLASSIC I) and 2; 55 patients in remission at both weeks 0 and 4 were re-randomised to adalimumab 40mg every other week, 40 mg weekly, or placebo for 56 weeks. Patients not in remission at both weeks 0 and 4 were enrolled in an open-label arm and received adalimumab 40 mg every other week. With non-response or flare, these patients could have their dosages increased to 40 mg weekly. Patients in the randomised arm with continued non-response or disease flare could switch to open-label adalimumab 40 mg every other week and again to 40 mg weekly. The primary endpoint was maintenance of remission in randomised

patients through week 56. Members noted that of 55 patients randomised at week 4, 79% who received adalimumab 40 mg every other week and 83% who received 40 mg weekly were in remission at week 56, v 44% for placebo ($p < 0.05$). In all, 204 patients entered the open-label arm. Of these, 93 (46%) were in clinical remission at week 56.

- 9.9 The Committee noted the new evidence presented relating to the current application. Sutharshan and Geary (J Crohns Colitis. 2013 Aug;7(7):e277-8) performed a prospective uncontrolled open label study in fourteen patients with Crohn's disease. Eight patients were female, two were current smokers, and nine were receiving thiopurine and two methotrexate. Disease location was ileal, colonic and ileocolonic in three, five and six patients, respectively, while disease behaviour was inflammatory stricturing and penetrating in three, seven and four patients, respectively. Five patients had perianal disease. Members noted that adalimumab was commenced in all patients with active disease (Crohn's disease activity index [CDAI]N300) not responding to or intolerant to an immunomodulator with induction of 160 mg, 80 mg fortnightly subcutaneously and then 40 mg fortnightly subcutaneously for remission. All patients initially responded (reduction of CDAI by N100) or achieved remission (CDAIb150) on adalimumab before relapsing (CDAI increase by greater than 100points). All patients were prescribed adalimumab 40 mg subcutaneously weekly for twelve weeks before returning to adalimumab 40 mg subcutaneously fortnightly. Nine out of fourteen Crohn's disease patients achieved CDAI 100 response or remission three months after reinstating fortnightly adalimumab. Median (range) follow-up (at the time the study was written) for these patients was 322 days (170–953) with eight remaining in response or remission. Members noted that of the initial five non-responders, two had surgery and three entered clinical trials of new biological agents with one of these patients eventually proceeding to surgery.
- 9.10 Members considered that in the absence of controls it was difficult to determine if patient response was solely attributable to adalimumab dose re-escalation or whether there were other confounding factors.
- 9.11 Members noted that they were not aware of any studies which compared weekly doses rescue therapy with maintenance on fortnightly treatments or with alternative treatment options such as re-introduction or dose escalation of corticosteroids.
- 9.12 The Committee considered the evidence to be of low strength and poor quality due to lack of controls, small patient numbers and high dropout rate (CHARM study).
- 9.13 The Committee considered that the majority of patients who receive dose escalation regain response. Members noted that it is unclear what the response rate related to the continuation of fortnightly treatment would be.
- 9.14 Members considered that weekly dosing could reduce or delay the use of infliximab, but considered that overall that this would be a cost to the health sector and pharmaceutical budget.
- 9.15 Members considered that the number of patients that are likely to receive adalimumab in preference to infliximab to be approximately 30%.
- 9.16 Members considered PHARMAC's estimate of the numbers of patients likely to lose remission and be candidates for weekly rescue therapy would be approximately 30%.

10 Adalimumab for the treatment of moderately to severely active ulcerative colitis

Application

The Committee considered an application from a supplier for the treatment of moderately to severely active ulcerative colitis in adult patients.

Recommendations

- 10.1 The Committee recommended that the application be declined because of limited evidence for sustained clinical effectiveness, lack of long term safety data and high financial risk.
- 10.2 The Committee recommended the application be referred to the Gastro-intestinal Subcommittee for further advice, including advice on the appropriate scoring scale for assessing disease severity.
- 10.3 The Decision Criteria particularly relevant to this recommendation are: (iii)The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv)The clinical benefits and risks of pharmaceuticals; (v)The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health & disability support service.

Discussion

- 10.4 The Committee noted that ulcerative colitis (UC) is a chronic inflammatory disease of the large intestine and that the cause of ulcerative colitis is unknown but genetic, immunological, dietary, and psychological factors have all been implicated. The Committee noted that that the clinical course varies and can be unpredictable. Members noted that the many patients present initially with highly active disease which then subsides to a milder form. The Committee noted that this submission related to patients who still have active disease despite being treated with standard therapy.
- 10.5 The Committee noted that the Simple Clinical Colitis Activity Index (SCCAI) (Walmsley, et al. Gut 1998 1998;43(1):29-32) has been widely adopted for use in New Zealand to assess disease severity and monitor patients during therapy. Members noted that SCCAI is different from the Mayo scoring system (Rutgeerts et al .N Engl J Med. 2005 Dec 8;353(23):2462-76) which is used in the clinical trials provided. Members noted that the SCCAI and Mayo scoring system are not interchangeable. The current threshold, SCCAI of ≥ 4 may reflect a less severe presentation than a Mayo score of ≥ 4 .
- 10.6 Members considered it appropriate to seek advice from the Gastrointestinal Subcommittee on whether SCCAI or the partial Mayo would be the most appropriate scale to use if adalimumab was to be funded for UC.
- 10.7 Members noted Tumor-Necrosis-Factor alpha inhibitors (TNFs) have been employed with some success in Crohn's disease (CD) and that TNFs are thought to have a prominent role in the inflammation associated with CD. Members noted however that the role of TNFs in UC was less clear and thus it was unclear whether

the experience with TNF from CD to UC can be extrapolated. Members noted that there is evidence of efficacy of infliximab in a severe UC population (Gisbert et al *Aliment Pharmacol Ther* 2006;25:19-37).

- 10.8 The Committee noted the clinical evidence presented in the submission consists of two pivotal randomised, double-blind, multicentre, placebo-controlled trials and one supportive on-going open label extension study.
- 10.9 The Committee noted the ULTRA 1 trial (Reinisch et al. 2011 *Gut* 2011;60:780-787). Patients with ulcerative colitis were initially randomised to adalimumab (160 mg/80 mg) or placebo at weeks 0 and 2, respectively. Subsequently, after an amendment of the protocol, a third arm, with adalimumab at 80 mg/40 mg, was included. All patients enrolled were naïve to anti-TNF α therapy and had active disease (defined by a full Mayo score of 6–12 and an endoscopic subscore of 2–3), despite stable doses of concomitant steroids, immunomodulators, or both. The primary endpoint, assessed in 390 patients with ulcerative colitis who were studied after the above amendment, was defined as the proportion of patients achieving clinical remission (full Mayo score \leq 2, with no individual subscore $>$ 1) by week 8 in each treatment arm. Week 8 clinical remission was achieved in 18.5% of patients in the adalimumab 160/80 mg group and in 9.2% of patients in the placebo arm ($P = 0.031$), showing a 9.3% of therapeutic gain. The week 8 clinical remission rate in the adalimumab 80/40 mg group was similar to that of the placebo group (10% vs 9.2%) ($P = 0.833$). The clinical response and mucosal healing among the three groups (secondary endpoints) were not significantly different. A post hoc analysis identified baseline clinical variables, such as extensive disease, high disease activity (Mayo score \geq 10) and high levels of systemic inflammation (C-reactive protein = 10 mg/L), that were associated with a low proportion of patients in clinical remission, which might reflect a lesser efficacy of adalimumab in patients with more severe disease. Thereafter, 390 patients entered an open-label extension study after week 8 and were maintained on adalimumab 40 mg every other week) for 52 weeks, with the possibility of dose-escalation to 40 mg weekly. A clinical remission at week 52 was reported in 25.6% of patients maintained with 40 mg of adalimumab every other week (EOW).
- 10.10 The Committee noted the ULTRA 2 trial (Sandborn et al. *Gastroenterology* 2012;142:257-265 494), where active ulcerative colitis patients were randomised to receive adalimumab 160 mg at week 0, 80 mg at week 2, and 40 mg EOW, or placebo, through to 52 weeks. The clinical and endoscopic eligibility characteristics were similar to those associated with the ULTRA 1 study, with the exception of the inclusion of ulcerative colitis patients (40% of the population studied) who had already experienced anti-TNF α agents, but with a discontinuation period of at least 8 weeks. The two co-primary endpoints were defined as the proportion of patients achieving clinical remission (defined as full Mayo score \leq 2, with no individual subscore $>$ 1) at week 8 and the proportion of patients achieving clinical remission at week 52. Members noted that the clinical remission at week 8 was achieved in 16.5% of patients in the adalimumab arm and in 9.3% of patients in the placebo arm ($P = 0.019$) (7.2% therapeutic gain). The corresponding values at week 52 were 17.3% and 8.5% ($P = 0.004$), respectively, with an absolute difference of adalimumab versus placebo of 8.8%. Moreover, a clinical response was achieved in 50.4% of patients receiving adalimumab and 34.6% on placebo ($P < 0.001$) at week 8 and in 30.2% and 18.3%, respectively ($P = 0.002$) at week 52. The benefit over placebo was also significant by endoscopic remission, evaluated at week 8 (41.1%, adalimumab vs 31.7%, placebo) ($P = 0.032$) and at week 52 (25% vs 15.4%, respectively) ($P = 0.009$). Members noted that a subgroup analysis, stratifying patients based on prior exposure to anti-TNF α , was also performed. Among naïve

patients, a week 8 clinical remission was achieved in 21.3% of patients in the adalimumab group and in 11% in the placebo group ($P = 0.017$); the corresponding values at week 52 were 22% and 12.4%, respectively ($P = 0.029$). A significant difference in clinical remission was found only at week 52 (10.2%, adalimumab and 3%, placebo) ($P = 0.039$) in the anti-TNF α -exposed group.

- 10.11 The Committee noted a post hoc intention-to-treat analysis of ULTRA 2 (Sandborn et al. *Aliment Pharmacol Ther* 2013;37:204–213) included all patients randomised to adalimumab who achieved a clinical response, as per their partial Mayo score at week 8, was performed to investigate week 52 clinical remission, response, mucosal healing, corticosteroid-free remission, and corticosteroid discontinuation rates. Members noted that among the 248 patients originally randomised to adalimumab, 123 (49.6%) had achieved clinical response. Of these, 30.9%, 49.6%, and 43.1% achieved clinical remission, clinical response, and mucosal healing at week 52, respectively. Of the 150 adalimumab-treated patients taking corticosteroids at enrolment, 90 (60%) responded, as per their partial Mayo score at week 8. Of these, 21.1% achieved corticosteroid-free remission and 37.8% were corticosteroid-free at week 52, without significant differences among the anti-TNF α -naïve and exposed patients.
- 10.12 The Committee considered the strength of the evidence was moderate for outcomes measured at 8 weeks. Members considered evidence to be weaker for long-term data and noted that UC is likely to be a long-term condition.
- 10.13 Members noted the high placebo effect associated with some trials.
- 10.14 Members noted that the efficacy of adalimumab and infliximab has not been directly compared, and that infliximab is the appropriate comparator for the cost-utility analysis.
- 10.15 Members noted that in a meta-analysis of studies that compared each of these anti-TNF agents with placebo, odds ratios for remission after 8 weeks of induction therapy were 5.26 (95% CI 2.94-9.99) for infliximab and 2.22 (95% CI 1.23-3.98) for adalimumab (Thorlund et al "Adalimumab versus infliximab for the treatment of moderate to severe ulcerative colitis in patients with no prior anti-TNF experience: An indirect comparison meta-analysis" *American College of Gastroenterology* 2013; Abstract P1030) Members noted that using Bayesian random-effect indirect comparison meta-analysis, the researchers then determined that the odds ratio for remission with adalimumab compared with infliximab was 0.42 (95% CI 0.17-0.97).
- 10.16 The Committee considered that there may be an increased risk of malignancy and infection associated with this patient population. Members considered that there was a need for longer term safety data for TNF therapies in ulcerative colitis.
- 10.17 Members considered infliximab to have a more rapid onset of action than adalimumab.

11 Sevelamer hydrochloride for hyperphosphataemia

Application

The Committee considered an update on the funding application by Sanofi-Aventis for sevelamer hydrochloride for the treatment of hyperphosphataemia.

Recommendation

- 11.1 The Committee **recommended** that the application for the funding of sevelamer hydrochloride be declined.
- 11.2 The Decision Criteria particularly relevant to these recommendations are: (i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (iv) The clinical benefits and risks of pharmaceuticals.

Discussion

- 11.3 The Committee noted that it had previously reviewed an application for sevelamer hydrochloride at their February 2013 meeting. It was noted that PTAC had recommended to decline the application at that meeting, and that the resubmission provided new information including a new trial, an updated meta-analysis, and added comments around the average daily dose, PTAC's previous minutes, and the price offered. Members noted that the resubmission proposed the same access restrictions as before.
- 11.4 The Committee noted the new ANZ registry data, showing that New Zealand is behind Australia in meeting targets for serum phosphate and serum calcium phosphate product.
- 11.5 The Committee considered the Di Lorio trial ([Am J Kidney Dis.](#) 2013 Oct;62(4):771-8. doi: 10.1053/j.ajkd.2013.03.023. Epub 2013 May 16) which was an open-label randomised controlled trial of over 400 people comparing sevelamer hydrochloride to calcium carbonate considering multiple mortality endpoints.
- 11.6 Members noted that hyperphosphataemia was not an entry criterion. The Committee considered that there were several important differences in the baseline statistics of the two arms, noting statistically significant differences in weight, serum phosphate, serum calcium, albumin, CRP, and dialysis adequacy. Members considered there to be a large difference in the coronary artery calcification (CAC) scores, particularly in that there were few patients with CAC > 400 in the sevelamer arm but many patients with CAC > 400 in the calcium arm. Members noted that CAC scores, had previously been associated with higher mortality .(Block GA et al Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 71:438-441) (Block GA et al Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int* **68**:1815-1824, 2005)
- 11.7 Members considered, given the study designers were aware of the association between CAC scores and mortality, that the arms should have been stratified by CAC score at baseline. Members similarly considered that patients should have been stratified by QT interval. Information on CAC scores in the trial arms was not

presented in the main journal article, being only in a graph in online supplementary material, and was not supplied by the applicant.

- 11.8 Members considered the statistical techniques used to analyse the results of Di Iorio et al's trial. They noted the use of a logarithm transformation to make CAC distribution more symmetric was inappropriate in this analysis setting. The Committee also considered the corrections to the study published online, and considered that these corrections should have been provided by the applicant in their resubmission.
- 11.9 The Committee considered the Jamal et al meta-analysis (Lancet 2013;382:1268-77) which members noted was an update to the analysis reviewed at the February meeting. This presents several analyses of "non-calcium binders", which mostly refers to sevelamer but includes a study of lanthanum, against calcium binders. Members considered that when the analysis included only RCTs, that although the overall estimate of effect favoured sevelamer, with a pooled risk ratio of 0.78 (95% CI 0.61 to 0.98) that only one of the RCTs had a statistically significant positive outcome. Members considered that the analysis only shows a mortality benefit at 24 months – not before or after. Members considered that this benefit is entirely due to the Borzeki trial which is a retrospective cohort analysis in which "laboratory values were missing in 50% of the calcium group and 70% of the sevelamer group" and which had multiple discrepancies in baseline characteristics. Members considered that analysis on dialysis status has a similar problem, and that analysis of CAC scores provides only a surrogate endpoint not sufficient to prove a mortality benefit.
- 11.10 The Committee did not consider that the new trial and analysis proves the assertions of a mortality benefit over other binders. Members noted that the resubmission does not address their original concerns around safety, with neither Di Iorio or Jamal considering adverse events. Members noted that, as before, they have only considered sevelamer hydrochloride, and they remain interested in seeing an application for sevelamer carbonate.

12 Dapagliflozin for type 2 diabetes

Application

The Committee considered an application from Astra Zeneca for dapagliflozin (Forxiga) for the treatment of type 2 diabetes.

Recommendation

- 12.1 The Committee **recommended** that 10mg dapagliflozin be funded with a low priority.

Discussion

- 12.2 The Committee noted that dapagliflozin is an oral, highly potent, selective and reversible sodium glucose co-transporter (SLGT2) inhibitor and has a unique mode of action in comparison to other funded pharmaceuticals for the treatment of hyperglycaemia associated with type 2 diabetes. The Committee noted that the mechanism of action was independent of beta cell function.

- 12.3 The Committee considered the evidence provided in the application to be of moderate to good strength and of high quality. The Committee noted there were no direct pioglitazone or insulin comparator studies provided.
- 12.4 The Committee considered and reviewed all evidence provided by the supplier and two systematic reviews provided by PHARMAC (Musso et al., *Ann Med.* 2012; 44: 375-394) (Clar et al., *BMJ Open.* 2012; 2(5): 1-12). Summaries of the key evidence are detailed.
- 12.5 Evidence provided included three placebo controlled trials with dapagliflozin as add on treatment to metformin (CT-014, CT-003, CT-012,), one placebo controlled trial with dapagliflozin as add on treatment to glimepiride (CT-005) and once active comparator trial with dapagliflozin versus glipizide as add on to metformin treatment (CT-004). The Committee noted that all placebo-controlled trials had a lead in period of two to four weeks and that rescue medication (acarbose, pioglitazone, metformin, DPP4-I, insulin) was provided for patients exceeding glycaemic limits in majority of trials. The Committee noted there were no Australian or New Zealand participants in the trials. The Committee noted that all outcomes in the trials were based on surrogate markers and no data on survival outcome was available.
- 12.6 A number of indirect comparisons with other oral anti-diabetic treatments and systematic reviews of studies with insulin initiation as an intervention were also noted.
- 12.7 The Committee considered a multicentre, randomised, double blind, placebo controlled study investigating the safety and efficacy of dapagliflozin as add-on therapy to metformin in patients with type 2 diabetes with inadequate glycaemic control (Bailey et al. *Lancet.* 2010; 375: 2223-2233). The primary outcome, the change from baseline in HbA1c at week 24, showed the mean HbA1c had decreased by 0.30% (95%CI -0.44 to -0.16) in the placebo group, compared with -0.84% (-0.98 to -0.70, $p < 0.0001$) in the 10mg dapagliflozin group. The Committee noted that hypoglycaemia occurred in similar proportions of patients in the dapagliflozin (2-4%) and placebo groups (3%). The Committee noted that genital infections were more frequent in the dapagliflozin groups (8-13%) than in the placebo group (5%), and did not result in discontinuation from the study.
- 12.8 The Committee considered the long term extension (102 weeks) of the 24 week randomized, placebo-controlled trial described above (Bailey et al, *BMC Medicine* 2013; 11(43): 1-10). The Committee considered that at week 102 mean changes from baseline HbA1c (8.08%) were +0.02% for placebo compared with -0.78% ($p < 0.0001$) for 10mg dapagliflozin.
- 12.9 The Committee considered a 52 week, double blind, active-controlled, non-inferiority study that randomised 814 patient with type 2 diabetes inadequately controlled with metformin (mean HbA1c 7.7%) to add on treatment with dapagliflozin or glipizide (Nauck et al., *Diabetes Care* 2011; 34(9): 2015-2022). The Committee considered that the mean reduction in HbA1c was similar in both groups (-0.52%). Dapagliflozin reduced weight (-3.2kg versus +1.2kg with glipizide) ($p < 0.0001$) and produced less hypoglycaemia (3.5% vs. 40.8% with glipizide) ($p < 0.0001$). The Committee noted the high discontinuation rates in both groups (just over 20%) were higher than the placebo controlled trials and noted that discontinuation was mainly due to lack of glycaemic control, withdrawal of consent, adverse events and failure to meet study criteria.

- 12.10 The Committee considered a randomised, double blind, placebo controlled study that investigated the effect on HbA1c of dapagliflozin or placebo as add on treatment to glimepiride. The Committee considered that after 24 weeks when added to glimepiride, adjusted mean difference in change from baseline HbA1c between dapagliflozin and placebo was -0.68 (95%CI -0.86 to -0.51, p <0.0001).
- 12.11 The Committee considered dapagliflozin to have an overall modest glucose lowering profile with similar potency to the DPP4 inhibitors and acarbose. The Committee considered the weight reduction associated with dapagliflozin to be modest, however the Committee noted that with the exceptions of metformin and acarbose the funded anti-diabetic medications are associated with weight gain. The Committee considered the blood pressure lowering effects of dapagliflozin to be modest.
- 12.12 The Committee considered that the efficacy of dapagliflozin is dependent on renal function and noted the manufacturers recommendations that dapagliflozin should not be used in patients with moderate to severe renal impairment eGFR <60ml/min/1.73m². The Committee considered renal impairment is a common comorbidity in patients with Type 2 diabetes and this may limit the use of the drug.
- 12.13 The Committee noted that patients with type 2 diabetes are at a higher risk of fungal genital infections and UTIs compared with the general population. The Committee considered the higher incidence of urinary and genital infections associated with dapagliflozin and considered that although these were generally mild-moderate and resolved with simple treatment, there would be a cost associated.
- 12.14 The Committee considered that although dapagliflozin appeared to be generally safe and well tolerated there was no long-term safety data at this time to fully exclude an increased risk of bladder/breast cancer.
- 12.15 The Committee considered the most likely place of dapagliflozin in therapy would be as a second-line agent when metformin and/or sulphonylurea were contraindicated/not tolerated, prior to insulin initiation. All patients prescribed dapagliflozin would need to have adequate renal function. The Committee considered that it would be used as an alternative to pioglitazone. The Committee noted that access to pioglitazone should not be removed from the treatment algorithm as it lowers HbA1c and is not contraindicated in renal impairment. The committee noted that the cost of dapagliflozin was [withheld on the basis of section 9(2)(b)(ii) of the Official Information Act ("commercial prejudice")] pioglitazone. The Committee noted that dapagliflozin would not replace insulin but would delay the need for insulin for the majority of patients that tolerated treatment.
- 12.16 The Committee considered the low risk of hypoglycaemia associated with dapagliflozin may be of benefit to patients who must avoid treatments which cause hypoglycaemia due to occupational risk. The Committee noted their previous request for the Diabetes Subcommittee to provide definitions around the occupational risk restriction proposed in previous special authority criteria for dipeptidyl peptidase-4 inhibitors and GLP-1 mimetics and **recommended** that the Diabetes Subcommittee provide advice on appropriate entry criteria for dapagliflozin.
- 12.17 The Committee noted proposed special authority restrictions from the supplier. The Committee considered that a restriction would be required to target therapy, and recommended that the Diabetes Subcommittee develop this.

- 12.18 The Committee **recommended** the Diabetes Subcommittee should develop a treatment algorithm for the available agents, including currently unfunded agents. The Committee requested advice from the Diabetes Subcommittee as to whether there were any specific class of unfunded hypoglycaemic agent that had a clinical advantage that would give one class a higher priority.

13 Omalizumab for allergic asthma

Application

The Committee considered an updated application from Novartis for omalizumab (Xolair) for the treatment of severe asthma.

Recommendation

- 13.1 The Committee **recommended** that omalizumab be funded for the treatment of severe asthma with a medium priority following the development of Special Authority criteria with strict entry and exit criteria and the facility for a trial of treatment.
- 13.2 The Decision Criteria particularly relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

Discussion

- 13.3 The Committee noted that omalizumab is a recombinant DNA-derived humanized monoclonal antibody, which selectively binds to the Ce3 domain of free IgE. This markedly decreases the level of free IgE and prevents its interaction with the high-affinity IgE receptor (FCεRI) on mast cells and basophils. By interrupting the allergic cascade, it targets the inflammatory processes of allergic asthma, as well as other IgE mediated disorders such as chronic idiopathic urticaria and possibly atopic eczema.

The Committee noted that, in New Zealand, omalizumab is indicated for the reduction of asthma exacerbations and control of asthma symptoms when given as add-on therapy for adult and adolescent patients, 6 years and older, with severe persistent allergic asthma who have IgE \geq 30 IU/mL, a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

- 13.4 The Committee noted that omalizumab had previously been considered by PTAC at its May 2007 meeting where it was referred to the Respiratory Subcommittee for further consideration. Omalizumab was considered at the June 2007 Respiratory Subcommittee meeting who recommended declining the application to list omalizumab. The Committee noted that the Respiratory Subcommittee reviewed an updated application from Novartis at its May 2013 meeting and recommended that omalizumab be listed on the Pharmaceutical Schedule with a medium priority and recommended that PHARMAC develop Special Authority criteria for treatment

of the small group of patients with severe allergic asthma that is not well controlled by other pharmaceuticals.

- 13.5 The Committee noted that in 2007 the Subcommittee expressed some concerns regarding the randomisation of patients in INNOVATE study (Allergy 2005; 60:309-16) and the combined outcomes used in the Ayers study (Allergy 2004; 59: 701-8). They also felt the Holgate study (Clin Exp Allergy 2004; 34: 632-8) did not show an improvement in asthma exacerbation rates.
- 13.6 The Committee noted that the updated application contained a number of clinical trials published since the 2007 application and reviewed these papers. The Committee noted that these trials showed that the asthma exacerbation rates were significantly lower in the patient populations that had been treated with omalizumab with rates reducing by 25 to 48%, that the pooled results suggest a 47% reduction in the rate of emergency room visits and that there was some corticosteroid sparing effect with one study showing a reduction in fluticasone use by 57% versus 43% when treated with optimal asthma therapy and another showing a 75% reduction versus 50% after 28 weeks. The Committee noted that the registry and real world studies largely showed clinical benefit with about 70% of patients showing a good response by week 16.
- 13.7 The Committee noted that there had been a number of NICE reports published with the most recent in April 2013 giving the following recommendations:
- 1.1 Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE mediated asthma as an add on to optimised standard therapy in people aged 6 years and older:
 - I. who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and
 - II. only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.
 - 1.2 Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high dose corticosteroids, long acting beta₂ agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.
 - 1.3 Patients currently receiving omalizumab whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.
- 13.8 The Committee noted that there had been a number of pharmacoeconomic studies published since 2007, the majority of which claim that omalizumab is cost effective.
- 13.9 The Committee noted the hospitalisation rates in New Zealand for patients classified under the hospital discharge data as being asthmatics (J45) or having status asthmaticus (J46), being treated with oral and inhaled corticosteroids. The Committee noted that 52 patients aged 6 to 44 years were identified as being on 12 plus months of oral corticosteroids plus inhaled steroids (ICS or ICS/LABA combination inhalers), and a further 1942 patients were on 4 or more courses of oral prednisone and inhaled inhalers although most of the 2nd group had not been hospitalised.

- 13.10 The Committee considered the quality of the studies was moderate and that they showed moderate to strong evidence of clinically significant benefits but that the studies may not have included patients with frequent hospitalisations. The Committee noted that there is some evidence of a persistent reduction in IgE levels.
- 13.11 The Committee also noted that there was a risk of anaphylaxis associated with the treatment with omalizumab and that the risk lasts for up to 3 days post treatment.
- 13.12 The Committee considered that there is a group of patients that would benefit from treatment with omalizumab and recommended funding of omalizumab for that group but recognised that identifying that group would be difficult.
- 13.13 The Committee **recommended** that PHARMAC develop Special Authority criteria that:
- Targets the population that would benefit the most (which may include reference to the number of hospitalisations in any one year and the level of severity of the hospitalisation)
 - Has strict entry and exit criteria based on IgE levels, hospitalisation rates and severity and corticosteroid use
 - Includes a trial period of 16 weeks
 - Has no renewal period so that patients may be assessed as to whether or not they require on-going treatment.