

## **PTAC meeting held held on 9 & 10 May 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.
- that any part of the minutes relating to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML) will be released, in a complete publication with the original Hospital Pharmaceuticals Subcommittee minutes and final recommendations made by PTAC, once PTAC have reviewed each therapeutic group.

PTAC may:

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

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

- (i) enable PHARMAC to carry out, without prejudice or disadvantage, commercial activities (section 9(2)(i)); and/or
- (ii) enable PHARMAC to carry on, without prejudice or disadvantage, negotiations, including commercial negotiations (section 9(2)(j));

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# 1 Matters Arising

## 1.1 Paliperidone depot injection – response to November 2012 PTAC Minutes

- 1.1.1 The Committee noted further correspondence and information from clinicians in support of paliperidone depot injection. The Committee again noted that paliperidone is the active metabolite of risperidone and, although members considered that there were potential preference benefits to patients and caregivers, the Committee considered that its previous recommendation, that paliperidone depot injection should be funded only if it was cost-neutral to risperidone depot injection, was appropriate, given that it was a very similar product with a different delivery mechanism.
- 1.1.2 The Committee felt that some of the purported benefits were overstated, for example members considered that paliperidone depot injection would be unlikely to reduce patient contact time by 50% and that many patients would need to be seen more frequently than every four weeks.
- 1.1.3 The Committee noted that the supplied literature suggested that paliperidone depot injection has an incidence of hyperprolactinaemia at least equal to that of the risperidone depot injection.
- 1.1.4 The Committee considered that, if it was funded, paliperidone depot injection would likely replace risperidone depot injection very quickly, including in patients already taking risperidone depot injection.
- 1.1.5 Ultimately, the Committee considered that this was primarily a cost issue for PHARMAC as there was little or no efficacy difference between the two products, and reiterated its previous cost-neutral recommendation.

## 1.2 Ticagrelor for acute coronary syndrome (ACS)

- 1.2.1 The Committee discussed the new proposed Special Authority criteria for ticagrelor in acute coronary syndromes, which essentially allows all patients with ST-elevation and non-ST-elevation myocardial infarction to access funded treatment. The Committee considered that it did not have clinical concerns with the new criteria and they would be simpler for clinicians to adhere to.

## 1.3 NZRA submission for rituximab for ANCA-associated vasculitides (ANCA-AAV)

- 1.3.1 The Committee noted correspondence from the New Zealand Rheumatology Association (NZRA) in response to previous PTAC minutes (February 2013) on rituximab in vasculitis.
- 1.3.2 The Committee considered the information provided by the NZRA, quantifying the risk associated with a cumulative dose of cyclophosphamide >15g. The Committee agreed that, based on the

available evidence, a 15g cut-off dose would be reasonable for cyclophosphamide in the rituximab Special Authority criteria.

- 1.3.3 Members noted that the NZRA disagreed with PTAC's previous recommendation, that the efficacy of mycophenolate was considered similar to rituximab in MPO-ANCA vasculitis. The NZRA considered that the evidence previously provided for mycophenolate did not include its use in patients with severe renal disease. The NZRA also noted that it would seek further advice from a renal physician in regards to mycophenolate in this patient group. The NZRA considered that renal physicians are more likely to see the severe spectrum of MPO-ANCA vasculitis and will be better placed to comment on the safety of mycophenolate in that setting.
- 1.3.4 The Committee noted that its previous recommendation was based on the evidence provided at that time and that it remained open to reviewing its recommendation when additional evidence is provided.
- 1.3.5 The Committee considered that it would be appropriate to proceed with its previous recommendation for rituximab to be funded with low priority subject to the following Special Authority criteria:

**ANCA associated vasculitis, rituximab-naïve**

*Limited to 4 weeks' treatment*

All of the following:

1. Patient has been diagnosed with ANCA associated vasculitis; and
2. Mycophenolate has not been effective in those patients who have MPO-ANCA positive vasculitis and
3. The rituximab dose would not exceed 375 mg/m<sup>2</sup> of body-surface area per week for a total of 4 weeks; and
4. Any of the following:
  - 4.1. Induction therapy with daily oral or pulse intravenous cyclophosphamide has failed to achieve complete absence of disease after 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
  - 4.3. Cyclophosphamide and methotrexate are contraindicated; or
  - 4.4. Patient is a woman of childbearing age; or
  - 4.5. Patient has a previous history of haemorrhagic cystitis, urological malignancy or haematological malignancy.

**ANCA associated vasculitis, prior rituximab use**

*Limited to 4 weeks' treatment*

All of the following:

1. Patient has been diagnosed with ANCA associated vasculitis; and
2. Patient has previously responded to treatment with rituximab but is now experiencing in an acute flare of vasculitis; and

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3. The rituximab dose would not exceed 375 mg/m<sup>2</sup> of body-surface area per week for a total of 4 weeks.

- 1.3.6 The Committee considered that MPO-ANCA positive vasculitis patients who have not trialled mycophenolate could be considered on a case-by-case basis through the Named Patient Pharmaceutical Assessment (NPPA) process until further evidence is provided to PTAC for rituximab in this patient group. The Committee also considered it appropriate to seek further advice from the renal physicians who originally submitted an application for this indication.

## **2 Subcommittee Minutes**

### 2.1 Gastrointestinal Subcommittee – 19 December 2012

- 2.1.1 The Committee noted and accepted the record of the meeting.

### 2.2 Immunisation Treatments Subcommittee (teleconference) – 12 February 2013

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

### 2.3 Immunisation Treatments Subcommittee – 6 March 2013

- 2.3.1 The Committee noted items 1 and 2.

- 2.3.2 Regarding item 3, the human papillomavirus (HPV) vaccine, the Committee noted and accepted the Subcommittee's recommendations for points 3.15 and 3.16:

- 3.15 The Subcommittee recommended that the age of female vaccination be amended to allow the first dose at age 11 with a medium priority, and allow the school based program to be initiated in year seven rather than year eight.

- 3.16 The Subcommittee recommended that a pilot study may be beneficial to assess the impact of a change to the school based programme prior to full rollout.

- 2.3.3 However members considered they would need to review the evidence with regards to points 3.17 and 3.18 before making a recommendation:

- 3.17 The Subcommittee recommended widening access to HPV vaccine to include males between the ages of 11 and 25 inclusive who identify as MSM with a high priority.

- 3.18 The Subcommittee recommended widening access to HPV vaccine to include all males between the ages of 11 and 18 with a low priority.

- 2.3.4 The Committee considered it should review the evidence before any changes to this market occur.
  - 2.3.5 Regarding items 4 and 5, the Committee considered that it needed to review the applications for rotavirus vaccine and varicella vaccine before it made a final formal recommendation. The Committee recommended that these be provided at the August meeting.
  - 2.3.6 PTAC noted that the vaccines currently on the National Immunisation Schedule are contracted until 1 July 2014 and that historically new vaccines were introduced in time with changes to the schedule. Decisions would need to be made by October 2013 to allow implementation of any changes for 1 July 2014.
  - 2.3.7 The Committee noted and accepted items 6 and 7.
- 2.4 Special Foods Subcommittee – Monday 27 August 2012
- 2.4.1 The Committee noted and accepted the record of the meeting.
- 2.5 Special Foods Subcommittee – Teleconference Wednesday 26 September 2012
- 2.5.1 The Committee noted and accepted the record of the meeting.

### 3 Correspondence

- 3.1 The Committee noted correspondence from Aspen Pharma regarding the PTAC minutes from 8 & 9 November 2012 for prolonged release melatonin 2mg. PTAC noted that PHARMAC requested information for indications other than primary insomnia. PTAC **recommended** that a footnote be added to reflect this.
- 3.1.1 PTAC noted that for primary insomnia, it maintained its view that melatonin slow release was as effective as zopiclone [withheld under s 9(2)(i) and 9(2)(j) of the OIA]
  - 3.1.2 PTAC noted that it reads and considers all the evidence provided, and though the minutes may not reflect everything read by Committee members they do reflect the discussions that occurred at the meeting. In this case, PTAC was most interested in the evidence for primary insomnia and behavioural disorders in children.
  - 3.1.3 PTAC noted that the minutes reflected the discussion that was had and its' final view, and as such could and should not be changed, other than the addition of a footnote.

## 4 Lenalidomide as third line treatment in multiple myeloma

### Application

- 4.1 The Committee reviewed an application from Celgene for the listing of lenalidomide on the Pharmaceutical Schedule for the treatment of multiple myeloma in two specific patient groups; as second line therapy in patients intolerant to either bortezomib or thalidomide, or in the third line setting in patients who have received previous treatment with bortezomib and thalidomide.

### Recommendation

- 4.2 The Committee **recommended** that lenalidomide be listed on the Pharmaceutical Schedule with:
- 4.2.1 high priority as second line therapy in patients with multiple myeloma who have developed significant peripheral neuropathy which prevents the continuation of treatment with either bortezomib or thalidomide; and
  - 4.2.2 low priority in the third line setting in patients who have received and failed previous treatment with bortezomib and thalidomide.
- 4.3 The Committee also **recommended** that the application be referred to the Cancer Treatments Subcommittee of PTAC (CaTSoP) for consideration and advice on appropriate Special Authority criteria.
- 4.4 The Decision Criteria particularly relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 4.5 The Committee noted that 275 new cases of multiple myeloma are registered in the New Zealand cancer registry each year; however, the true incidence of multiple myeloma may be higher. The Committee noted that the median age at diagnosis is 70 years old, and that if a patient is diagnosed at 60 years they have a 10 year overall survival rate of 30%. The Committee noted that overall survival has significantly improved in recent years (Palumbo A. Cancer 2007;110:824-829). The Committee noted that multiple myeloma is incurable and that almost all patients who respond to treatment will eventually relapse and require further treatment.
- 4.6 The Committee noted that eligible patients undergo stem cell transplants, and that patients who are not eligible for stem cell transplant are currently usually treated with bortezomib with melphalan and prednisone. Following relapse, patients are likely to

receive thalidomide and dexamethasone or chemotherapy. Patients are able to access funded bortezomib in the second-line setting if they did not receive it in the first-line setting.

- 4.7 The Committee noted that lenalidomide is an analogue of thalidomide, and is used in combination with dexamethasone. The Committee noted that lenalidomide also had similar risk of teratogenicity as thalidomide and those patients, prescribers and pharmacists must meet the conditions of the lenalidomide access program before being prescribed the drug.
- 4.8 The Committee noted two main studies: 009 (Weber et al. NEJM 2007;357:2133-2142) and 010 (Dimopoulos et al. NEJM 2007;357:2123-2132), that were phase III, randomised, double-blinded control trials.
- 4.9 The Committee noted in Study 009 that 353 patients were enrolled, and that 177 were randomised to receive lenalidomide with dexamethasone and 176 patients were randomised to receive placebo with dexamethasone. The Committee noted that the groups were well matched, with 62% from each treatment group having at least two previous treatments. Randomised patients received either lenalidomide or placebo on days 1-21 of each 28 day cycle with dexamethasone on days 1, 4, 9-12, 17 and 20. Time to progression was 11.1 months with lenalidomide compared with 4.7 months in patients who received dexamethasone only ( $p < 0.001$ , hazard ratio (HR) 0.27-0.47). In patients who previously received thalidomide the median time to progression was 8.5 months with lenalidomide and 4.1 months in the dexamethasone only group; this result was not statistically significant ( $p = 0.08$ ). In patients who previously received bortezomib, time to progression was 10.3 months compared with 3.3 months in the dexamethasone group ( $p < 0.001$ ). The Committee noted that interim overall survival (at May 2006) was 29.6 months in the lenalidomide group and 20.2 months in the dexamethasone only group (HR 0.44 95% confidence intervals (CIs) 0.3-0.65,  $p < 0.001$ ).
- 4.10 The Committee noted that 62% of patients had previous stem cell transplants, 10% had previously received bortezomib, and 43% had previously received thalidomide. The Committee noted that this was different to the New Zealand population, as in New Zealand most patients will have received bortezomib. The Committee noted that 21.5% of patients in the lenalidomide group had infections compared with 12.5% in the dexamethasone only group, although this difference was not statistically significant. Most of the infections were urinary tract or pneumonia. In the placebo arm, grade 3 or 4 effects occurred at 1.1%, 0% and 0% for peripheral neuropathy, constipation or diarrhoea respectively. Venous thromboembolism occurred more frequently in the lenalidomide group compared with the dexamethasone only group (14.7% versus 3.4%,  $p < 0.001$ ). The dose of lenalidomide was reduced in seven patients, and was stopped in eight patients after they had venous thromboembolism. The Committee noted that grade 3 or 4 neutropenia and thrombocytopenia events were significantly more likely to occur in patients receiving lenalidomide compared with dexamethasone only (41.2% vs 4.6%,  $p < 0.001$  for neutropenia and 14.7% vs 6.9%,  $p = 0.02$  for thrombocytopenia).
- 4.11 The Committee noted that in Study 010 there were 351 patients; 176 received lenalidomide with dexamethasone, and 175 received placebo with dexamethasone.



The Committee noted they received the same dosing as in the 009 Study. The Committee noted that the groups were well matched, and that approximately 67% had received at least two therapies. Half of the patients had previous stem cell transplant, only 4% had previously been treated with bortezomib, and approximately one third had previously received thalidomide.

- 4.12 The Committee noted that a pre-specified interim analysis was undertaken after 111 patients had progressed, and that crossover was allowed. Intention-to-treat analysis was used. The Committee noted an increase in time to progression of 11.3 months in the lenalidomide group, compared with 4.7 months in the dexamethasone group ( $p < 0.001$ ). The Committee noted that within the lenalidomide group, there was no statistically significant difference in time to progression based on previous thalidomide use (HR 0.65, 95% CI 0.42-1.02,  $p = 0.06$ ). Interim overall survival data from May 2006 was 20.6 months in the dexamethasone only group, and median overall survival was not reached in the lenalidomide group.
- 4.13 The Committee noted grade 3 or 4 neutropenia occurred in 3.4% of patients in the lenalidomide group compared with none in the dexamethasone only group. Grade 3 or 4 thrombocytopenia was more likely to occur in patients receiving lenalidomide compared with dexamethasone only (11.4% vs 5.7%). Deep vein thrombosis and pulmonary embolism were more common in the lenalidomide group (8.5% vs 4.7%).
- 4.14 The Committee noted updated overall survival data information from the 009 and 010 studies published in 2009 by Dimopolous et al, cited above. The Committee noted that the pooled data contained information of 704 patients with extended median follow-up of 48 months for overall survival. Overall survival was defined as time from randomisation to death from any cause. Median survival was 38 months in the lenalidomide group compared with 31.6 months in the dexamethasone only group ( $p = 0.045$ ). The Committee noted that progression free survival was 11.1 months for lenalidomide compared with 4.6 months for dexamethasone only ( $p < 0.001$ ).
- 4.15 The Committee noted that the aim of the Stadmauer et al. (Eur J Haematol 2009;82:426-432) study was to compare outcomes from patients receiving lenalidomide after one line of treatment with those having more than one line of treatment in patients in the 009 and 010 trials. Patients with one previous treatment tended to have a higher overall response rate compared with patients who had two or more previous treatments for multiple myeloma (66.9% vs 56.8%,  $p = 0.06$ ). The Committee noted that time to progression was significantly longer in patients who had only received one previous treatment (17.1 months vs 10.6 months, HR 0.68, CI 0.48-0.97,  $p = 0.026$ ).
- 4.16 The Committee noted a trial by Gay et al. (Blood 2010;115:1343-1350) in newly diagnosed multiple myeloma patients that compared patients who received lenalidomide with dexamethasone to patients who received thalidomide with dexamethasone. The Committee noted that peripheral neuropathy associated with lenalidomide was 0.9% in the added lenalidomide group compared with 10.4% in the added thalidomide group ( $p < 0.001$ ). The Committee noted that this reduction in peripheral neuropathy could be very important for some patients.

- 4.17 The Committee noted that it had previously reviewed an application for lenalidomide as second-line treatment in patients with relapsed or refractory multiple myeloma in August 2009; and in February 2010 the Committee agreed with CaTSoP's low priority recommendation for funding. The Committee noted that the current application was for lenalidomide in the third-line setting, as bortezomib had since been funded on the Pharmaceutical Schedule for multiple myeloma.
- 4.18 The Committee noted that the evidence to support third line use of lenalidomide is not as strong as its use in the second line setting in patients who were intolerant to either thalidomide or bortezomib. The Committee noted that retreatment with either bortezomib or thalidomide is likely to be equally effective as a third line treatment. The Committee noted that there are not many effective treatments for third line use, and that lenalidomide could be useful in this setting.
- 4.19 The Committee noted that other than lenalidomide drug costs, there could be changes in health sector expenditure due to the monitoring of toxicities, as well as additional red cell platelet transfusions and increased erythropoietin usage. However, this may be offset by a reduction in chemotherapy use.

## 5 Influenza antivirals

### Application

- 5.1 The Committee reviewed an application from PHARMAC for advice on the use of neuramidase inhibitors (NIs) for the prevention and treatment of seasonal influenza.

### Recommendation

- 5.2 The Committee **recommended** neuramidase inhibitors (NIs) be listed on the Hospital Medicines List with the following restriction:

Inpatient use only where patient has confirmed or suspected influenza; or  
For inpatient treatment as part of infection control strategy according to a DHB approved infection control plan

- 5.3 The Committee **recommended** neuraminidase inhibitors not be listed on the Community Pharmaceutical Schedule.
- 5.4 The Decision Criteria particularly relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## Discussion

- 5.5 The Committee noted that PHARMAC had not included neuraminidase inhibitors (NIs) in Section H. The Committee noted that the decision was inconsistent with international advice from the National Institute of Clinical Excellence (NICE technology appraisal guidance 58) and the Centres for Disease Control and Prevention (CDC report MMWR 2011;60(1)), regarding their recommendations for the prevention and treatment of seasonal influenza in community dwelling patients.
- 5.6 The Committee noted that two neuraminidase inhibitors are currently registered – oseltamivir and zanamivir. Both agents are registered for the treatment and prophylaxis of influenza.
- 5.7 The Committee noted PHARMAC had consulted the Section H list which did not include NIs. PHARMAC had received correspondence from a hospital clinician who requested that oseltamivir be listed on the HML for use during the influenza season, according to local annually reviewed guidelines.
- 5.8 The Committee noted that there have been a number of key systematic reviews published on the efficacy and safety of these agents when used for the treatment and prophylaxis of seasonal influenza (Jefferson et al. Cochrane Database Syst Rev 2012;1:CD008965; Burch et al. Health Technol Assess 2009;13:1-265; Burch et al. Lancet Infect Dis 2009;9:537-545; Hernán & Lipsitch. Clin Infect Dis 2011;53:277-279; Tappenden et al. Health Technol Assess 2009;13:1-246; and Wang et al. Cochrane Database Syst Rev 2012;4:CD002744).
- 5.9 The Committee noted the extensive literature evaluating the efficacy of NIs when used for prophylaxis and treatment of hospitalised patients with suspected or confirmed influenza, including pre and post exposure chemoprophylaxis and patients in intensive care.
- 5.10 Members noted that, despite the large amount of literature relating to NIs when used to treat influenza, randomised controlled trial (RCT) data is only available for patients treated in the community. This evidence indicates that patients administered oseltamivir within 48 hours of developing influenza-like symptoms had a reduction in the duration of symptoms by 20.7 hours [95% CI 13.3 to 28.0 hours] (Ebell et al. Fam Pract 2013;30:125-133). However, no statistically significant difference was found in the time to alleviation of symptoms in elderly patients or those with chronic diseases.
- 5.11 Members further considered that intention-to-treat for influenza (ITTI) studies, suggesting reductions in durations of symptoms, were possibly flawed. The reduction may have been due to the possible impact of oseltamivir on the serological response, leading to reduced odds of being diagnosed with influenza. Members noted Professor Tom Jefferson's view (Cochrane Database Syst Rev 2012;1:CD008965) that due to the potential impact of oseltamivir on serological response, all influenza comparisons are potentially confounded by the actions of the drug.
- 5.12 The Committee considered that there is insufficient RCT evidence to address whether treatment with NIs reduced the risk of complications, hospitalisations and mortality in patients with influenza. PTAC noted that studies were conducted primarily amongst

previously healthy outpatients with uncomplicated influenza; therefore the effect of treatment in serious or life-threatening influenza is uncertain. The Committee noted that this issue has been raised in several reviews, including the Cochrane Group (Cochrane Database Syst Rev 2012;1:CD008965), the CDC (MMWR 2011;60(RR-1)) and the most recent meta-analysis by Ebell et al. (Fam Pract 2013;30:125-133).

- 5.13 The Committee noted the evidence for the role of NIs in the hospital setting relies on non-randomised observational studies and expert opinion. However, these agents are widely used in the hospital setting despite the lack of high quality evidence. It was noted that there is no published evidence on the efficacy of oseltamivir in elderly hospitalised patients. Members considered that oseltamivir has also become the mainstay of influenza treatment in the critical care setting.
- 5.14 The Committee considered that the evidence for prophylaxis for post exposure to influenza is more robust. Members noted a systematic review by Tappenden et al. (Health Technol Assess 2009;13:1-246), which found that oseltamivir was effective in preventing symptomatic laboratory-confirmed influenza in households of mixed composition (RR 0.19, 95% CI 0.08-0.45). The efficacy of zanamivir in post-exposure prophylaxis within households was also reported (RR 0.21, 95% CI 0.13-0.33). The Committee noted that there is no evidence for at-risk adults or elderly patients.
- 5.15 The Committee noted that NIs are currently the only anti-viral agents for influenza and that amantadine is not effective due to resistance problems.
- 5.16 The Committee noted that within the hospital system there are currently no problems with access to NIs for prophylaxis or treatment of influenza.
- 5.17 The Committee noted that international guidelines recommend early antiviral treatment of suspected or confirmed influenza among persons with severe influenza-like symptoms, such as those patients who have severe, complicated or progressive illnesses who require hospitalisation. The Committee considered the numbers of people in this group within a standard seasonal influenza is likely to be low.
- 5.18 The Committee noted that very few DHBs are using NIs for post exposure prophylaxis.
- 5.19 The Committee noted that Māori are at increased risk of COPD and pneumonia and thus are potentially at greater risk of influenza complications.
- 5.20 Members considered that there was no need to restrict access any further than what is currently employed. The Committee considered that there is awareness in clinical practice of the low quality of the evidence base. The Committee considered that NIs would be prescribed judiciously in the hospital setting for both treatment and prophylaxis of influenza.
- 5.21 The Committee considered that the funding of NIs should be restricted to patients admitted to hospital. These patients are likely to have more severe forms of influenza and/or are at high risk of influenza complications. The Committee considered that the benefits of NIs were limited, and that there is currently insufficient evidence of benefit (beyond a reduction of time to alleviation of symptoms) to recommend wider funding.

- 5.22 The Committee considered that the length of treatment for post exposure prophylaxis within the hospital setting would be unlikely to exceed 10 days. The Committee considered that this would only be used in Infection Control Situations as part of a plan approved by DHB hospitals with Infectious Disease input.

## **6 Dexrazoxane for cardioprotection in chemotherapy in paediatrics**

### **Application**

- 6.1 The Committee reviewed an application from the National Child Cancer Network for the funding of dexrazoxane in: patients enrolled in randomised clinical trials of cancer chemotherapy, children under 5 years at high risk of cardiac toxicity from anthracycline therapy, children up to 19 years with evidence of cardiac toxicity, and patients who have received a high dose of anthracycline therapy.

### **Recommendation**

- 6.2 The Committee **recommended** that dexrazoxane be funded for paediatric cancer patients participating in a randomised clinical trial.
- 6.3 The Committee **recommended** that the funding of dexrazoxane for adult patients and for paediatric cancer patients not participating in a randomised clinical trial, including those treated as per trial protocols, be declined.
- 6.4 The Committee **recommended** that PHARMAC actively engage in wide discussions with paediatricians and paediatric oncologists regarding the mechanism through which paediatric oncology treatments are reviewed and funded.
- 6.5 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals.*

### **Discussion**

- 6.6 The Committee considered that the strength of evidence is weak to moderate in children and moderate to strong in adults, and that the evidence is of moderate quality in both age groups. In adults, members noted two meta-analyses of adults that both cover the same six randomised controlled trials (Smith. BMC Cancer 2010;10:337; and van Dalen. Cochrane 2011;6:CD003917). In children, members identified one published RCT (Lipshultz. NEJM 2004;351:145-153) as well as another partially reported RCT (POG-9494, Salzer. Leukemia 2010;24:335-344).
- 6.7 The Committee considered that there is no evidence that the use of dexrazoxane increases life expectancy. Members noted that neither the van Dalen Cochrane review nor the Lipshultz study reported a difference in either overall survival or progression-free survival. Members also noted that the POG-9404 study is not fully available and so overall survival data is not yet published, but that 10-year event-free survival is worse in the dexrazoxane group.

- 6.8 The Committee considered that in studies considering whether dexrazoxane reduced anthracycline-related cardiac toxicity, there was evidence of publication bias. Further, studies in this area were predominantly in patients with breast cancer with a median age of 55, meaning they were not appropriate for the indication and patient groups being considered. Members considered that in the older breast cancer group there is moderate evidence of a strong effect to reduce cardiac toxicity, while in children there is weak evidence of a weak to moderate effect to reduce cardiac toxicity. Members considered this evidence weak because of unmasked treatment and high drop-out rates. The Committee noted that there were no clinical trials looking specifically at the effectiveness and safety of dexrazoxane.
- 6.9 Members considered that there is some evidence that dexrazoxane increases secondary malignancies in children. Members noted that the POG-9404 study reported increased secondary malignancies in children taking dexrazoxane, although the full results of this study remain unpublished. Members considered that there was a four-fold relative risk of secondary malignancies in a follow-up of about 10 years.
- 6.10 The Committee noted that while dexrazoxane is approved by the European Medicines Agency for use in the European Union, its use is restricted to adult patients with advanced or metastatic breast cancer and is contraindicated for children and adolescents up to the age of 18 years. The Committee also noted that dexrazoxane is still commonly used in the USA and that many randomised controlled trials conducted by American research organisations require patients to take dexrazoxane as part of treatment protocol.
- 6.11 Members considered that it is beneficial for patients to participate in clinical trials, as participating in a clinical trial offers a high standard of care from more intensive trial-protocol monitoring and follow-up. Members noted that such trials, especially ones undertaken by non-profit research organisations rather than pharmaceutical companies, often do not fund the cost of dexrazoxane. Members considered that if patients do not have publicly-funded dexrazoxane, then they may not be able to participate in these trials.
- 6.12 Members noted that for most adult clinical trials run by research groups or organisations other than pharmaceutical companies, the cost of medicines including supportive treatments are met as part of the trial funding. Members noted that this is not the situation with paediatric oncology trials, where all medicine costs need to be met by DHBs. Members considered that there are currently few limitations to access to paediatric oncology products, unlike in the adult setting. Members consider that this presents an equity issue. The Committee noted that PHARMAC intends to review the mechanism through which paediatric oncology treatments are reviewed and funded.
- 6.13 In light of PHARMACs increasing role in hospital pharmaceuticals for all paediatric patients the Committee recommended that PHARMAC actively engage in wide discussions with paediatricians, and paediatric oncologists, regarding the mechanism through which paediatric oncology treatments are reviewed and funded.
- 6.14 The Committee made a recommendation for dexrazoxane to be funded for paediatric patients enrolled in oncology trials, despite considering dexrazoxane itself to have no clear benefit and some evidence of harm. Members stressed that the positive

recommendation was based on providing young patients with access to US-run, international collaborative clinical trials, and that health gains are expected to be achieved by participating in the trial itself rather than from the effects of dexrazoxane.

## 7 Erlotinib for NSCLC, stage IIIB/IV, EGFR mutation, first-line

### Application

- 7.1 The Committee reviewed an application from Roche New Zealand for the funding of erlotinib hydrochloride for first line treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.

### Recommendation

- 7.2 The Committee **recommended** that erlotinib hydrochloride be listed on the Pharmaceutical Schedule for first line treatment, under the same Special Authority criteria as gefitinib, only if cost-neutral to gefitinib.
- 7.3 The Committee **recommended** that the Special Authority criteria for second line usage of erlotinib hydrochloride to be implemented 1 January 2014, be amended to remove the criterion “Insufficient biopsy sample available to determine EGFR mutation status or precise histological type”.
- 7.4 The Decision Criteria particularly relevant to these recommendations are: *(ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government’s overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 7.5 The Committee noted evidence from two multicentre, open label, randomised phase 3 trials, in patients with EGFR-mutation positive (exon 19 deletion or L858R mutation in exon 21) NSCLC with no previous history of chemotherapy: the EURTAC trial (Rosell et al. Lancet Oncol 2012;13:239-246) and the OPTIMAL trial (Zhou et al. Lancet Oncol 2011;12:735-742). The EURTAC trial was conducted in a European population, which is closer to the New Zealand population than the other main tyrosine kinase inhibitor (TKI) trials such as the OPTIMAL which were carried out in Asian populations. The Committee noted that it is generally recognised that Asian EGFR positive patients respond better to TKIs. The Committee considered that the trials were generally well conducted and applicable to the NZ population, but were open-label trials with relatively small numbers. It was noted that there was no central reviewing of imaging in the OPTIMAL trial, which due to the lack of blinding, could create bias. The EURTAC trial reported significantly longer progression free survival (PFS) and higher response rates with erlotinib compared with two standard chemotherapy regimes. There was not a significant overall survival (OS) advantage but the OS data was contaminated by

extensive crossover at time of progression. OPTIMAL indicated better PFS and response rate advantages compared with EURTAC but OS was not significantly better with erlotinib compared with chemotherapy (probably due to extensive crossover at progression).

- 7.6 The Committee noted evidence from an indirect comparison of erlotinib with gefitinib. A pooled analysis of erlotinib and gefitinib (Paz-Ares et al. J Cell Mol Med 2010;14:51-69), which did not include the two phase 3 trials using erlotinib, suggested that both erlotinib and gefitinib may be more effective than chemotherapy in patients with EGFR mutations. The results of the pooled analysis suggested PFS of 13.2 months for erlotinib and 9.8 months with gefitinib, however not all studies used were for the first line indication. An update of this, presented at the 2012 European Society of Medical Oncology (ESMO) conference, included the most recent phase 3 trial data and reported PFS of 12 months for erlotinib versus 9.8 months for gefitinib. The Committee noted that there were additional limitations with the indirect comparison (beyond standard methodological limitations), including different data sets, different ways of measuring PFS, different patient groups, and the presence of many small disparate trials.
- 7.7 The Committee noted the economic evaluation provided by the supplier. The Committee considered that the assumed dose of 142.1 mg from the EURTAC trial and that the chemotherapy comparisons based on trial data were both reasonable. The adverse events frequency was also considered to be reasonable. The frequency of general practitioner visits for rash may be higher than modelled due to warnings regarding rashes with erlotinib, but the Committee considered this would not likely be a large additional cost.
- 7.8 The Committee considered that erlotinib (150 mg daily) and gefitinib (250 mg daily) have the same or similar effect and could be considered under the same therapeutic sub-group which would allow for reference pricing between the two chemicals.
- 7.9 The Committee considered that the Special Authority for second line usage of erlotinib hydrochloride, to be implemented 1 January 2014, should be amended to remove the criterion "Insufficient biopsy sample available to determine EGFR mutation status or precise histological type", as core needle biopsy sampling should be standard practice by 2014. The Committee expressed concern that if this criterion was not amended it would result in significant fiscal risk.

## **8 Tocilizumab for refractory adult onset Still's disease**

### **Application**

- 8.1 The Committee considered an application from the New Zealand Rheumatology Association (NZRA) for the funding of tocilizumab for refractory adult-onset Still's disease (AOSD).

### **Recommendations**

- 8.2 The Committee **recommended** that tocilizumab be listed on the Pharmaceutical Schedule for AOSD as an alternative to tumour necrosis factor (TNF) inhibitors, subject

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to the following restrictions and review of these restrictions by the Rheumatology Subcommittee, only if it was cost neutral to the TNF inhibitors (etanercept and adalimumab):

**Initial application - (adult-onset Still's disease) only from a rheumatologist.**

Approvals valid for 4 months for applications meeting the following criteria:

All of the following:

- 1 Patient diagnosed with adult onset Still's disease (AOSD) according to the Yamaguchi criteria (J Rheumatol 1992;19:424-430); and
- 2 Patient has tried and not responded to at least 6 months of glucocorticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and methotrexate; and
- 3 Patient has persistent symptoms of disabling poorly controlled and active disease.

**Renewal - (adult-onset Still's disease) only from a rheumatologist or Practitioner on the recommendation of a rheumatologist.** Approvals valid for 6 months for applications meeting the following criteria:

Both:

- 1 Either:
  - 1.1 Applicant is a rheumatologist; or
  - 1.2 Applicant is a Practitioner and confirms that a rheumatologist has provided a letter, email or fax recommending that the patient continues with tocilizumab treatment; and
- 2 The patient has a sustained improvement in inflammatory markers and functional status.

8.3 The Committee **recommended** that tocilizumab for AOSD be listed on the Pharmaceutical Schedule for AOSD after TNF inhibitors, subject to the following restrictions, with a low priority:

**Initial application - (adult-onset Still's disease) only from a rheumatologist.** Approvals valid for 4 months for applications meeting the following criteria:

Both:

- 1 The patient has had an initial Special Authority approval for etanercept or adalimumab for adult-onset Still's disease (AOSD); and
- 2 Either:
  - 2.1 The patient has experienced intolerable side effects from etanercept or adalimumab; or
  - 2.2 The patient has received insufficient benefit from at least a three-month trial of etanercept or adalimumab such that they do not meet the renewal criteria for AOSD.

**Renewal - (adult-onset Still's disease) only from a rheumatologist or Practitioner on the recommendation of a rheumatologist.** Approvals valid for 6 months for applications meeting the following criteria:

Both:

- 1 Either:
  - 1.2 Applicant is a rheumatologist; or
  - 1.3 Applicant is a Practitioner and confirms that a rheumatologist has provided a letter, email or fax recommending that the patient continues with tocilizumab treatment; and
- 2 The patient has a sustained improvement in inflammatory markers and functional status.

8.4 The Committee further **recommended** that if tocilizumab was listed for AOSD under either scenario, the criteria for adalimumab and etanercept should be amended to permit their use in AOSD subject to criteria essentially outlined under the Committee's first recommendation, above.

8.5 The Decision Criteria particularly relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of*

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

## **Discussion**

- 8.6 The Committee noted that the term AOSD describes adults who do not fulfil all the criteria for diagnosis of rheumatoid arthritis but have clinical features and biomarkers similar to children with systemic-onset juvenile idiopathic arthritis (sJIA). Members noted that the clinical classification of juvenile idiopathic arthritis (JIA) has an essentially arbitrary age cut-off so patients who develop clinical markers as adults do not meet this definition. The Committee considered that it would not be appropriate for a patient diagnosed with AOSD (e.g. according to the Yamaguchi criteria (J Rheumatol 1992;19:424-430) to access a TNF inhibitor via the JIA criteria or to access tocilizumab via the sJIA criteria. The Committee considered that this should be made clear in any notification of a decision to list tocilizumab for sJIA.
- 8.7 The Committee noted that tocilizumab is registered for use in rheumatoid arthritis and sJIA, but not specifically for AOSD.
- 8.8 The Committee noted that current treatment options for AOSD are non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate. The Committee noted that some patients eventually meet the criteria for biologic treatments (TNF inhibitors) for rheumatoid arthritis.
- 8.9 The Committee reviewed a number of case series reports for biologic treatments in AOSD for TNF inhibitors, infliximab and anakinra (Husni et al. Arthritis Rheum 2002;46:1171-1176; Kraetsch et al. Ann Rheum Dis 2001;60 Suppl 3:iii55-iii57; Fautrel et al. Ann Rheum Dis 2005;64:262-266; Kötter et al. Semin Arthritis Rheum 2007;37:189-197). The Committee considered that these reports provided low-quality evidence for limited efficacy of these treatments in AOSD, although the TNF inhibitors appeared to be less effective for AOSD than for patients with rheumatoid arthritis. Patients with systemic features appear to be less responsive to the TNF inhibitor treatments.
- 8.10 The Committee noted that tocilizumab is a recombinant humanised monoclonal antibody that binds to interleukin (IL)-6 receptors, thereby inhibiting IL-6 receptor-mediated signalling. Members noted that IL-6 is elevated in AOSD.
- 8.11 The Committee noted that in November 2011 it had recommended listing tocilizumab in the Pharmaceutical Schedule for sJIA with a high priority, based on randomised controlled trial evidence from the TENDER trial (De Benedetti et al, NEJM. 2012; 367(25):2385-2395). The Committee noted that PHARMAC had recently consulted on a proposal to list tocilizumab for sJIA, although a funding decision was still pending.

- 8.12 The Committee noted a case series of 14 patients with AOSD treated with tocilizumab over a 3 year period (Puechal et al. *Arthritis Care Res* 2011;63:155-159). All patients were refractory to methotrexate and anakinra and 12 had previously tried one TNF inhibitor. Half the patients had systemic features. Dosing regimens varied. Eleven patients completed 6 months follow-up, two withdrew due to side effects, and one had a systemic flare. At 6 months the mean disease activity score (DAS) reportedly reduced from 5.61 to 2.91, the European League Against Rheumatism (EULAR) remission was achieved by 57% of patients, 86% of patients had resolution of systemic symptoms, and mean prednisone dose reduced from 23.3 mg/day to 10.3 mg/day.
- 8.13 The Committee noted a case series of seven patients with AOSD treated with tocilizumab (Muraviev et al. *Ann Rheum Dis* 2012;71(Suppl 3):672), in which joint and systemic symptoms reportedly improved for all patients.
- 8.14 The Committee noted a retrospective uncontrolled survey of 16 cases of AOSD treated with biologics on 24 occasions (Suematsu et al. *Modern Rheumatol* 2012;22:712-719). Eleven patients had systemic features and all but one patient reportedly responded to tocilizumab.
- 8.15 The Committee noted an unpublished report (in abstract form, Elkayam et al. *Am Coll Rheum* 2012; abstract 193) of 11 patients with AOSD with systemic features, seven of whom had previously had a TNF inhibitor. After 15 months none had systemic symptoms and two had mild arthralgia.
- 8.16 The Committee noted a number of other case reports, each involving two or three patients with AOSD who responded to tocilizumab (Thonhoffer et al. *Rheumatol Int* 2011;31:1653–1656; Cunha et al. *Rheumatol* 2010;49:1014–1016; Rech. *Ann Rheum Dis* 2011;70:390-392; Sato et al. *Arthritis Res & Ther* 2012;14(Suppl 1):P62; Sakai et al. *Clin Rheumatol* 2012;31:569-574); Boysson et al. *Clin Rheumatol* 2013;32:141-147). Members noted several other reports of single case studies and some articles reviewing other reports of case studies.
- 8.17 Overall, the Committee considered the strength of evidence for the effectiveness of tocilizumab in AOSD was moderate but the quality of the evidence was poor as it consisted largely of small case series reports and there were no controlled studies in AOSD.
- 8.18 The Committee considered there was unmet need for treatments for patients with refractory AOSD who do not meet the criteria for TNF inhibitors for RA. The Committee considered that tocilizumab may be more effective than TNF inhibitors for AOSD, but there was no good evidence to support this. Therefore, the Committee considered that if access was to be widened to biologic treatments for AOSD, it would be reasonable to widen access to TNF inhibitors and tocilizumab with the same access criteria only if tocilizumab was the same net price as the TNF inhibitors. The Committee considered it would be reasonable to position tocilizumab after TNF inhibitors if it was more expensive.
- 8.19 The Committee considered that, if it was listed for AOSD, tocilizumab could be used in combination with glucocorticosteroids, NSAIDs and methotrexate. Members considered that the patient group most likely to benefit from tocilizumab was AOSD patients with

systemic features, refractory to treatment with NSAIDs, steroids and DMARDs. Members considered that the use of tocilizumab may enable tapering the use of steroids and would likely replace the use of TNF inhibitors if it was available with equal access.

- 8.20 The Committee considered that the additional risks from tocilizumab treatment are difficult to quantify due to the poor quality of the evidence. Tocilizumab could be associated with macrophage activation syndrome (MAS), psoriasis, and an increase in liver derangement (including but not confined to increased need for liver function testing), infections and cytopenias.
- 8.21 The Committee considered that, for the purposes of PHARMAC analyses, the quality of life of patients with severe refractory AOSD should be assumed to be similar to that of SJA rather than rheumatoid arthritis, due to the frequent systemic features of AOSD.
- 8.22 The Committee considered that the estimated patient numbers of 23 per year seemed reasonable, although members noted that a diagnosis of AOSD might be more frequent than this and it would be important to ensure that any access criteria include a definition of the diagnosis of AOSD using the Yamaguchi criteria.

## 9 Nicotine inhaler and oral spray for smoking cessation

### Application

- 9.1 The Committee reviewed an application from PHARMAC, with supporting information from DHBs, the Ministry of Health, and the supplier, for the listing of nicotine inhaler and oral spray on the Pharmaceutical Schedule; in the community for people trying to quit smoking ('smoking cessation'), and in DHB hospitals for smokers without access to facilities where they can smoke but who do not intend quitting smoking ('urge control').

### Recommendations

- 9.2 The Committee **recommended** that the application for nicotine inhalers and oral spray for smoking cessation use in the community be declined.
- 9.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*
- 9.4 The Committee **recommended** that nicotine inhalers and oral spray be listed in Section H of the Pharmaceutical Schedule, with high priority for urge control in patients in psychiatric wards, perioperative patients, and other agitated patients while in hospital.

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

## **Discussion**

### *Smoking Cessation*

- 9.6 The Committee noted that smoking is associated with considerable disease burden of both premature mortality and morbidity. The Committee noted that nicotine is highly addictive and there are significant physical and psychological withdrawal symptoms. The Committee noted that there are several funded medicines to aid in smoking cessation, including nicotine replacement therapy ((NRT): nicotine patches, gum and lozenges), nortriptyline, bupropion and varenicline. The Committee noted that these options are all currently available and funded on the Pharmaceutical Schedule.
- 9.7 The Committee considered that a 2012 Cochrane review (Stead et al. Cochrane Database Syst Rev 2012;11:CD000146) provides the best clinical evidence of the efficacy of nicotine inhalers and oral spray on smoking cessation. The Committee noted that the Cochrane review included studies that compared the inhaler and oral spray with placebo and with other formulations of NRT, as well as their use in combination with other formulations of NRT. The Committee noted that the additional benefit from quitting smoking with NRT compared with no NRT or placebo was 7% (relative risk [RR] 1.6, 95% CI 1.53-1.68). The Committee noted that all formulations of NRT were superior to placebo, and considered that the effect size of nicotine oral spray and inhaler was similar to nicotine lozenges.
- 9.8 The Committee noted that there were limited studies, with small patient numbers, that looked at combination NRT treatment compared with placebo. The Committee noted that the use of nicotine patch with nicotine inhaler was not significantly better than placebo (RR 1.07 95% CI 0.57-1.99) (Stead et al. 2012).
- 9.9 The Committee noted that the Cochrane review suggested that there was no significant difference in quit rates between nicotine lozenge and nicotine patches; however, the combination of lozenge and patch significantly improved the quit rate when compared with the patches alone (Stead et al. 2012).
- 9.10 The Committee noted a randomised, placebo controlled study of nicotine nasal spray plus patches versus patches alone (Blondal et al. BMJ 1999;318:285-288) in which abstinence outcomes were validated by carbon monoxide levels in 237 patients. This study reported a significant increase in sustained abstinence rate with nicotine nasal spray plus patch compared with patch alone (RR 2.48 95% CI 1.37-4.49) and a significant difference persisting in 6 year follow-up.
- 9.11 The Committee noted an analysis in the Cochrane review where two studies compared the nicotine nasal spray with nicotine patches as monotherapy and reported no statistically significant difference in quit rates (RR 0.9, 95% CI 0.64-1.27) (Stead et al. 2012).

- 9.12 The Committee considered a randomised controlled trial that compared a nicotine inhaler (13 µg/puff) with a placebo inhaler in 400 patients (200 in each treatment arm) (Bolliger et al. *BMJ* 2000;321:329-333). The Committee noted that this study showed a significant difference in the primary outcome measure of '50% or greater reduction in daily cigarette use' that was sustained (OR at 24 months 3.39, 95% CI 1.39-8.29,  $p=0.012$ ). The Committee noted there was a modest difference in abstinence at four months; 13% vs 4% (OR 3.41, 95% CI 1.16-10.01,  $p=0.044$ ). However, by 12 months the results no longer differed significantly (OR 1.26, 95% CI 0.65-2.47,  $p=0.609$ ).
- 9.13 The Committee noted a study by Rennard et al. (*Nicotine Tob Res* 2006;8:555-564) in which 429 patients who smoked more than 20 cigarettes per day were randomised to receive either a 10 mg nicotine inhaler ( $n=214$ ) or placebo inhaler ( $n=215$ ). The primary endpoint of the study was a reduction in smoking. The Committee noted that there was a high dropout of patients in the trial (275/429) over the 15 month period. The analysis was intention-to-treat where dropouts were considered to be smokers who had not reduced the number of cigarettes smoked per day. The Committee noted there was a significant effect on the quit rate at 12 months; 7.9% of patients who received the nicotine inhaler remained abstinent, compared with 2.3% of those who received placebo ( $p=0.014$ ). The Committee noted that the average numbers of inhalers used did not appear to reduce over the 12 month study period. The Committee noted there was little improvement in quality of life apart from self-control.
- 9.14 The Committee highlighted a study included in the Cochrane review which compared nicotine gum or inhaler with placebo (Kralikova et al. *BMC Public Health* 2009;9:433). Patients were volunteers who had smoked 15 cigarettes or more each day for at least 3 years. In this trial, patients were allowed to choose between nicotine gum or inhaler; 84% patients chose the inhaler. The Committee noted this indicates there could be a strong preference for this preparation if funded. The primary outcome measured in the trial was a sustained reduction in smoking (greater than 50%) or abstinence. The Committee noted there was a significant effect on the proportion of smokers abstinent (18.7% vs 8.6% at 12 months  $p=0.009$ ) but not on the proportion with sustained reduction of smoking in the active arm compared with placebo.
- 9.15 The Committee noted an open-label randomised controlled trial of four different NRT regimens; 5 mg patch ('control arm'); 15 mg patch; nicotine inhaler; and nicotine inhaler with 15 mg patch (Tønneson et al. *Respir J* 2000;16:717-722). The Committee noted that the 15 mg patch was significantly more effective than other regimens, with a 12 month sustained quit rate of 8.7% vs 1.8% ( $p<0.05$ , logistic regression), while sustained quit rates were not significantly different in the other arms (5.1% and 3.5% for inhaler, and inhaler plus 15 mg patch).
- 9.16 The Committee noted that the side effects from nicotine inhalers and oral spray include nausea and dizziness as well as mouth or throat irritation (Medsafe datasheet).
- 9.17 Overall, the Committee considered that the inhaled nicotine preparations are better than placebo at reducing smoking consumption, and they can lead to on-going reduction in the number of cigarettes smoked as well as increased abstinence. However, the Committee considered that there is no strong evidence that inhaled preparations are clinically more effective than any other form of NRT. The Committee

considered that it was possible that abstinence could improve if inhaled preparations were used in combination with nicotine patches.

- 9.18 The Committee considered that patients could remain on the inhalers long-term (i.e. patients could become addicted to the inhalers) if they were funded, although members noted that this would probably be better for the individual than smoking cigarettes.
- 9.19 The Committee considered that uptake of nicotine inhaler and oral spray would be high if they were funded and they would be used in preference to (or in combination with) other funded NRT formulations. The Committee considered that this would be associated with considerable additional NRT expenditure, given that these preparations are more expensive than the currently funded formulations. The Committee considered, however, that there was no good evidence to suggest that either the inhaler or the oral spray presentation was more effective than the currently funded formulations in terms of sustained quit rates, even taking patient preference into account.

#### *Urge Control*

- 9.20 The Committee noted that it is difficult for hospital staff treating patients who wish to smoke in mental health services without access to facilities where they can smoke. There are other situations in hospitals where nicotine inhalers or oral spray may be better than community funded NRT formulations for use in smokers, for example in patients who have to fast before surgery (because chewing nicotine gum stimulates saliva secretion, adversely increasing aspiration risk in anaesthesia), or in agitated patients unable to leave hospital facilities in order to smoke (which could also pose a risk to hospital staff of verbal or physical assault).
- 9.21 The Committee noted unpublished pharmacokinetic data provided by the supplier to support a more rapid rise in circulating nicotine when administered by inhaler as opposed to lozenge, and that this would more closely approximate the pharmacokinetics of nicotine from smoked tobacco. These data support the idea that nicotine inhalers and sprays might be more effective than lozenges or gum for urge control.
- 9.22 The Committee noted a non-blinded randomised controlled trial of nicotine lozenges (2 mg and 4 mg) and a nicotine oral spray (Hansson et al. *BMJ Open* 2012;2(5). pii: e001618). The trial studied the urge to smoke, which was measured on a visual analogue scale. The Committee noted that all preparations reportedly reduced the urge to smoke, and that the oral spray reduced the urge more than lozenges (within the first 10 minutes).

- 9.23 The Committee noted the Medicines and Healthcare Products Regulatory Agency (MHRA) assessment of the oral spray, which noted a pharmacokinetic difference between the oral spray and the lozenge or gum (MHRA, Nicorette Quickmist 1mg/spray mouthspray PL15513/0357 <http://www.mhra.gov.uk/home/groups/par/documents/websitesources/con194682.pdf>). The Committee noted that this could likely more quickly reduce the urge to smoke, but would require more frequent use to control the urge to smoke.
- 9.24 The Committee noted that there was no high quality evidence for the use of nicotine inhaler or oral spray for urge control in the hospital setting, although it is biologically plausible from pharmacokinetic data that the inhaler and oral spray would be beneficial in terms of quicker onset of effect.
- 9.25 The Committee noted that the price of the inhaler was significantly less than the oral spray and that it may, therefore, be preferable to fund only the inhaler.

## 10 Cetuximab for locally advanced head and neck squamous cell carcinoma

### Application

- 10.1 The Committee reviewed an application from Merck Serono for the use of cetuximab for patients with locally advanced squamous cell cancer of the head and neck (who are considered medically unsuitable for chemotherapy treatment with cisplatin).

### Recommendation

- 10.2 The Committee **deferred** making a recommendation on cetuximab for patients with locally advanced squamous cell cancer of the head and neck (who are considered medically unsuitable for chemotherapy treatment with cisplatin).
- 10.3 The Committee **recommended** that the application be referred to CaTSoP for consideration. In particular, the Committee seeks the advice of CaTSoP regarding: the potential population size of the patient group that would be unsuitable for platinum-based therapies; the impact of renal impairment on the efficacy of cetuximab; the relevance of the evidence to the proposed patient group; and the patient group most likely to benefit.
- 10.4 The Decision Criteria particularly relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*



## Discussion

- 10.5 The Committee considered the overall strength of evidence to be moderate, with only one RCT demonstrating efficacy. Members noted that the study population is somewhat different to the proposed population in the proposal and that there was no data on number of patients in RCT who were unsuitable for radiotherapy (RT) with chemotherapy.
- 10.6 The Committee noted that based on Australian data, the supplier has estimated an annual incidence of patients with locally advanced disease at 143 patients. The Committee also noted that the supplier, based on clinician opinion, considered that 30% of this group would potentially be unsuitable for platinum-based chemotherapy which would give an estimated annual incidence of 43 patients in New Zealand.
- 10.7 The Committee considered that the application failed to adequately reflect the potential role of carboplatin as an alternative for patients where cisplatin is contraindicated. The Committee identified clinical trial data comparing the efficacy of carboplatin with RT to cetuximab with RT.
- 10.8 The Committee members considered that some, or perhaps all patients intolerant to cisplatin may be suitable to receive carboplatin therapy and thus fewer patients would benefit from cetuximab. The Committee considered that specialist input from CaTSoP would be useful to clarify whether the population requiring treatment was patients intolerant to cisplatin alone (as proposed by the supplier) or patients intolerant or contraindicated to all platinum-based therapies.
- 10.9 PTAC further commented that a common reason for platinum not being suitable was renal impairment. PTAC noted that it had not been presented with evidence relating to the use of cetuximab in patients with renal impairment. The Committee considered that the possibility of renal contraindications to the use of cetuximab may further reduce the number of patients potentially benefitting from cetuximab.
- 10.10 In the proposed indication, the Committee noted that the evidence for the clinical effectiveness of cetuximab plus RT is based on a single multinational clinical trial of 424 patients with locoregionally advanced cancers of the oropharynx, hypopharynx, or larynx, randomly assigned to RT with or without concurrent weekly cetuximab (Bonner et al. NEJM 2006; 354:567-578), specifically stage-III or IV nonmetastatic squamous cell carcinomas. Patients were assigned to high-dose radiation alone (213 patients) or high dose radiation with weekly cetuximab at an initial dose of 400 mg/m<sup>2</sup> administered 1 week before the start of RT, followed by 250 mg/m<sup>2</sup> weekly for the duration of the radiation. The Committee noted that blinding of participant patients and clinicians was not possible because cetuximab causes an acneiform rash, but outcomes were assessed by a blinded independent committee. The primary endpoint was the duration of control of locoregional disease; secondary end points were overall survival, progression-free survival, the response rate, and safety. The Committee noted that the median duration of locoregional control was 24.4 months for patients treated with the combination versus 14.9 months for those treated with RT alone (hazard ratio (HR) for locoregional progression or death 0.68, p=0.005). Members noted that median overall survival was 49.0 versus 29.3 months (HR for death 0.73, 95% CI 0.56-0.95, p=0.018). The 5-year survival was 45.6% in the cetuximab plus RT group versus 36.4% in the

RT-alone group with a median follow-up of 54 months, the cetuximab-treated group experiencing significantly better overall survival compared with RT alone (3-year survival 55% versus 45%, HR 0.73). The Committee noted results reported for median duration of loco-regional control according to site, with oropharyngeal cancer (49 vs. 23 months) reporting better outcomes than for laryngeal cancer (12.9 vs. 11.9 months) and hypopharyngeal cancers (12.5 vs. 10.3 months). However, members noted that efficacy between sites was not pre-specified in the trial, nor was the trial powered to detect a difference between the groups.

- 10.11 The Committee noted a recent update of the Bonner trial that reported 5-year survival, investigated the relationship between cetuximab-induced rash and survival, and undertook other subgroup analyses (Bonner et al. Lancet Oncol 2010;11:21-28). Overall survival in patients treated with cetuximab was significantly improved in those who experienced an acneiform rash of at least grade 2 severity compared with patients with no rash or grade 1 rash (HR 0.49, 0.34-0.72; p=0.002). However members noted that analysis of response based on rash was not pre-specified. In other subgroup analysis, oropharyngeal tumours, early T stage, advanced N stage, concomitant boost, high Karnofsky performance score (KPS) (90-100%), male sex, and age 65 years or younger were factors associated with a potential improvement in survival when cetuximab was added to RT. Members noted that the trial authors state that the trial was not powered for this subgroup analysis, and therefore that the data should be interpreted with caution.
- 10.12 The Committee noted another study, RTOG 1016, which is currently ongoing. The study is a Phase III trial of radiotherapy plus cetuximab versus cisplatin chemoradiotherapy in HPV-associated oropharynx cancer. Members noted that this study could provide an indication of the comparative efficacy of these two treatments.
- 10.13 The Committee recommended that, based on the available evidence, the use of cetuximab should be restricted to patients whose comorbidities render them medically unsuitable for all types of platinum-based chemoradiation therapy, or patients intolerant to platinum-based chemotherapy. Patient who have a high KPS score, have no distant metastases and oropharyngeal disease appear to benefit the most from cetuximab treatment.

## 11 Cetuximab for K-RAS wild type metastatic colorectal cancer

### Application

- 11.1 The Committee reviewed an application from Merck Serono for the listing of cetuximab for the treatment of KRAS wild-type metastatic colorectal cancer (mCRC). The Committee also reviewed a submission from the Gastrointestinal Cancer Special Interest Group for cetuximab for this indication.

### Recommendation

- 11.2 The Committee **deferred** making a recommendation on cetuximab in KRAS metastatic colorectal cancer.

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

## Discussion

- 11.5 Members noted that the funding applications from Merck Serono and Gastrointestinal Cancer Special Interest Group (GISIG) were for different patient groups. The Committee noted that Merck Serono proposed cetuximab use in a pre-surgical setting, while GISIG proposed cetuximab use as an 'end-of-line' treatment (detailed below).
- 11.6 The Committee noted that the supplier proposed that cetuximab funding be limited to patients meeting all of the following criteria:
1. KRAS wild-type metastatic colorectal cancer; and
  2. metastases confined to the liver only; and
  3. neoadjuvant chemotherapy treatment prior to surgical resection of liver metastasis is planned; and
  4. cetuximab to be used in addition to irinotecan-based neoadjuvant chemotherapy.
- 11.7 The Committee noted that the GISIG had recommended access to cetuximab be restricted to patients meeting all of the following criteria:
1. EGFR-expressing, K-RAS wild-type metastatic colorectal cancer; and
  2. cetuximab is to be given as single agent or in combination with irinotecan-based chemotherapy; and
  3. the patient has documented progression following and/or is intolerant to treatment with both oxaliplatin and irinotecan based therapy; and
  4. the patient has performance status 0-1; and
  5. cetuximab to be discontinued at disease progression; and
  6. approvals would be valid for 3 months.
- 11.8 The Committee noted a study by Van Cutsem et al. (NEJM 2009;360:1408-1417), CRYSTAL, which investigated the efficacy of cetuximab plus irinotecan, fluorouracil, and leucovorin (FOLFIRI) as first-line treatment for metastatic colorectal cancer. A post

hoc analysis tested for and examined associations between the mutation status of the KRAS gene in tumors and clinical response to cetuximab. The trial assigned patients with epidermal growth factor receptor-positive colorectal cancer with unresectable metastases to receive FOLFIRI either alone or in combination with cetuximab. The primary end point was progression-free survival. 599 patients received cetuximab plus FOLFIRI, and 599 received FOLFIRI alone. The hazard ratio for progression-free survival in the cetuximab-FOLFIRI group compared with the FOLFIRI group was 0.85 (95% CI 0.72-0.998, p=0.048). There was no significant difference in the overall survival between the two treatment groups (HR 0.93, 95% CI 0.81-1.07, p=0.31).

- 11.9 Members noted that there was a significant interaction between treatment group and KRAS mutation status for tumour response (p=0.03) but not for progression-free survival (p=0.07) or overall survival (p=0.44). The Committee noted the hazard ratio for progression-free survival among patients with wild-type-KRAS tumours was 0.68 (95% CI, 0.50 to 0.94), in favour of the cetuximab-FOLFIRI group. The Committee noted that the authors of the study considered that first-line treatment with cetuximab plus FOLFIRI, as compared with FOLFIRI alone, reduced the risk of progression of metastatic colorectal cancer. The reported benefit of cetuximab was limited to patients with KRAS wild-type tumours.
- 11.10 The Committee noted an updated analysis of the CRYSTAL study for overall survival, with a median duration follow-up of 29.9 months, according to tumour KRAS and BRAF mutation status (Van Cutsem et al. J Clin Oncol 2011;29:2011-2019). The Committee noted post study crossover was allowed, complicating extended overall survival analysis, and KRAS ascertainment was post hoc and unbalanced between the arms (60 vs 66%). The Committee noted that the addition of cetuximab to FOLFIRI in patients with KRAS wild-type disease resulted in statistically significant improvements in median overall survival (23.5 v 20.0 months; HR 0.796, p=0.0093), median progression-free survival (9.9 v 8.4 months, HR 0.696, p=0.0012), and response rate (57.3% v 39.7%; OR 2.069; p<0.001) compared with FOLFIRI alone. The Committee noted that there were significant interactions between KRAS status and treatment effect for all key efficacy end points. KRAS mutation status was reportedly confirmed as a powerful predictive biomarker for the efficacy of cetuximab plus FOLFIRI.
- 11.11 The Committee noted the CELIM randomised phase 2 trial study (Folprecht et al. Lancet Oncol 2010;11:38-47). This study considered tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab. Retrospective, blinded surgical review of patients with radiological images at both baseline and during treatment was performed to objectively assess any changes in resectability. Members noted that in a retrospective analysis of response by KRAS status, a partial or complete response was noted in 47 (70%) of 67 patients with KRAS wild-type tumours versus 11 (41%) of 27 patients with KRAS-mutated tumours (OR 3.42, 95% CI 1.35-8.66, p=0.0080). The Committee noted that according to the retrospective review, resectability rates increased from 32% (22 of 68 patients) at baseline to 60% (41 of 68) after chemotherapy (p<0.0001).
- 11.12 The Committee noted a study by Folprecht et al (Ann Oncol 2005;16:1311-1319) which analysed the correlation between tumour response and resection rates. The Committee noted that authors reported a strong correlation between response rates and the resection rate in patients with isolated liver metastases (r = 0.96, p=0.002). However

there was no significant association with rates of liver resection with curative intent (R0 resection) ( $r=0.43$ ). The Committee noted that studies were only included if the results of first line therapy were reported separately or if the proportion of second line treatment patients was low. The Committee also noted that the study suggested that patient selection and efficacy of pre-operative chemotherapy are both strong predictors for resectability of liver metastases.

11.13 The Committee noted the following trials, which reinforced the suggestion that KRAS mutational status was highly predictive in relation to the efficacy of cetuximab:

1. The OPUS study (Bokemeyer et al. Ann Oncol 2011;22:1535-1546)
2. Bokemeyer et al. J Clin Oncol 2009;27:663-671.

11.14 The Committee noted the Medical Research Council COIN trial, published as Maughan et al. (Lancet 2011;377:2103-2114), which considered the addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer. The Committee noted that of the three main trials this was the only one that pre-specified KRAS testing in the primary outcome analysis. The Committee noted that this trial did not confirm a progression free or overall survival benefit from addition of cetuximab to oxaliplatin-based chemotherapy in first-line treatment of patients with advanced colorectal cancer. Members noted that cetuximab reportedly increased “complete or partial” response rates (not further defined in the publication), with no evidence of benefit in progression-free or overall survival in KRAS wild-type patients or even in patients selected by additional mutational analysis of their tumours. Members noted the authors’ view that the use of cetuximab in combination with oxaliplatin and capecitabine in first-line chemotherapy in patients with widespread metastases cannot be recommended.

11.15 The Committee considered that overall it was difficult from the evidence available to adequately estimate the gains in liver resection rates likely to be observed and the extent of consequent gains in overall survival, if any. The Committee noted a poster by Kohne ([http://www.gisliides.com/slides/ASCO\\_2012\\_files/Koehne%20Cetux%20liver%20lim%20poster%20ASCO%202012.pdf](http://www.gisliides.com/slides/ASCO_2012_files/Koehne%20Cetux%20liver%20lim%20poster%20ASCO%202012.pdf)) which presented the differences in the rates of R0 – liver only metastasis resection rates with curative intent – in the KRAS wild type subpopulations in both the CRYSTAL and the OPUS trials, and noted that the poster indicated the direction of effect to be in favour of the cetuximab arms (but without statistical significance). Members considered that the evidence signalled that a gain was possible, but that this gain appeared small, the signals were not adequately strong, and that that the signals of benefit for bevacizumab in this setting were stronger. Members considered the health gains suggested by the supplier to be unrealistically optimistic. The Committee considered that if cetuximab were to be funded, access criteria should mandate clinical review at 16 weeks or earlier, on whether liver resection should occur and that if no resection was planned then funded cetuximab treatment be stopped.

11.16 The Committee noted that there may be some benefit from cetuximab treatment as an end-of-line treatment but it would essentially be a very expensive palliative treatment. The Committee also noted that the results from EPIC study (Sobrero et al. J Clin Oncol 2008;26:2311-2319) indicated that the addition of cetuximab to irinotecan in patients

with mCRC previously treated with fluoropyrimidine and oxaliplatin did not prolong overall survival, with only small gains in progression free survival.

## 12 Bevacizumab for metastatic colorectal cancer – first-line treatment

### Application

- 12.1 The Committee reviewed an application from Roche for the funding of bevacizumab (Avastin) in first-line metastatic colorectal cancer (mCRC) in combination with fluoropyrimidine-based chemotherapy until progression.

### Recommendation

- 12.2 The Committee **recommended** that funding of bevacizumab for all first-line metastatic colorectal cancer patients be declined.
- 12.3 The Committee restated its low-priority **recommendation** of February and August 2010 to fund bevacizumab as a first-line, neoadjuvant (pre-surgical), treatment in patients with metastatic colorectal cancer, where metastases are confined to the liver only, complete resection is planned, and funding is for a maximum of 4 treatment cycles.
- 12.4 The Decision Criteria particularly relevant to this recommendation are: *(i) the health needs of all eligible people within New Zealand; (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) the clinical benefits and risks of pharmaceuticals; (v) the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; 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

- 12.5 The Committee noted that this is the third application from Roche regarding bevacizumab, and that PTAC and its Subcommittees have considered the product several times, going back to 2005. The Committee noted that the current application relates to the same indication as the first application, unlike the second which proposed a narrower indication.
- 12.6 The Committee noted that their most recent recommendation on this indication was in 2006, when the Committee recommended to decline the proposal. Members noted two significant new pieces of information since that time.
- 12.7 The first new piece of information noted by the Committee was the publication of the NO16966 study (Saltz et al. J Clin Oncol 2008;26:2013-2019). This Phase III trial compared bevacizumab + XELOX or FOLFOX-4 therapy with XELOX or FOLFOX-4 therapy alone in 1,401 first-line mCRC patients. The study reported a statistically-

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significant increase in median time to progression-free survival (9.4 months vs 8.0 months, Hazard Ratio 0.83, 97.5% CI 0.72-0.95, p=0.002). The study also reported a non-statistically-significant increase in median overall survival (21.3 months vs 19.9 months, HR 0.89, 97.5% CI 0.76-1.03, p=0.077).

- 12.8 The second new piece of information noted by the Committee was the publication of a meta-analysis that considered the NO16966 study trial along with four other trials (Welch et al. *Annals Oncol* 2010;21:1152-1162). Members noted that, unlike the Saltz et al trial, this meta-analysis reported a statistically significant reduction in mortality (HR 0.79, 95% CI 0.69-0.90, p=0.0005).
- 12.9 The Committee considered that it could be appropriate to assume the level of benefit to overall survival reported in Saltz et al, although any analysis should account for the uncertainty. Members considered that the benefit to overall survival was low and uncertain, with Saltz et al reporting only an average of 6 weeks extended survival. Members considered that evidence was weak for the use of bevacizumab in combination with oxaliplatin.
- 12.10 The Committee considered that the cost-effectiveness reported by the applicant was poor relative to other proposals considered by PHARMAC. The Committee recommended that any cost-utility analysis performed by PHARMAC should use more conservative assumptions around benefits and extrapolation of data beyond the Saltz et al trial period.
- 12.11 The Committee considered that the patient population that would benefit most from bevacizumab would be the patient population considered in its meetings of February and August 2010. Members noted that funding for this indication had been declined by PHARMAC based on cost-effectiveness, in part due to the number of required doses being higher than previously thought. The Committee noted that the net price offered in the latest application is lower than previously offered.

## 13 Febuxostat for gout

### Application

- 13.1 The Committee considered an application from TeArai BioFarma for the listing of febuxostat (Adenuric) on the Pharmaceutical Schedule for the treatment of gout.

### Recommendation

- 13.2 The Committee **recommended** that febuxostat be listed in the Pharmaceutical Schedule with a medium priority, subject to Special Authority criteria. The Committee considered that if the pricing was similar to benzbromarone the following Special Authority criteria should apply, but if it was more expensive than benzbromarone it would be reasonable to further restrict it to be used after benzbromarone or where benzbromarone was contraindicated.

**Initial application** from any relevant practitioner. Applications valid for 6 months for applications meeting the following criteria:

Either:

1. The patient has a serum urate level greater than 0.36 mmol/l despite treatment with allopurinol at doses of at least 600 mg/day and appropriate doses of probenecid; or
2. The patient has experienced intolerable side effects from allopurinol such that treatment discontinuation is required and serum urate remains greater than 0.36 mmol/l despite appropriate doses of probenecid.

**Renewal** from any relevant practitioner. Applications valid for 2 years for applications where the treatment remains appropriate and the patient is benefitting from treatment.

- 13.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals.*

## Discussion

- 13.4 The Committee noted that gout is a significant public health issue and that the prevalence of gout among Pacific and Māori men, in particular, is high compared with non-Pacific and non-Māori Caucasian men.
- 13.5 The Committee noted that the ultimate goals of urate-lowering treatment is to prevent, or reduce the frequency of, acute gout attacks and reduce the size and/or number of clinically detectable urate crystal deposits (tophi).
- 13.6 The Committee noted that there are currently three fully funded urate-lowering treatments in New Zealand for the long-term management of gout: allopurinol (a xanthine oxidase inhibitor that inhibits production of urate), probenecid (a uricosuric agent that promotes urate excretion from the renal tubules) and benzbromarone (a bezofuran derivative that increases urinary uric acid excretion and is available funded as a third-line treatment option).
- 13.7 The Committee noted that all the funded treatments were generally well tolerated, but all have potentially treatment-limiting side effects: allopurinol is associated with skin rash (in up to 2% of patients) and severe and life-threatening hypersensitivity reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis in about 1 in 56,000 patients; probenecid has a propensity to cause nephrolithiasis and is generally not effective in patients with moderate to severe renal impairment; and benzbromarone is associated with potentially life-threatening hepatotoxicity in approximately 1 in 17,000 patients. The Committee noted that benzbromarone was not registered (but available supplied under section 29 of the Medicines Act 1981), and expressed its preference for registered products to be funded. The Committee noted that the current supplier of funded benzbromarone was intending to seek registration for this product.
- 13.8 The Committee noted that febuxostat is a non-purine, selective xanthine oxidase inhibitor that inhibits uric acid production by preventing the normal oxidation of purines to uric acid. The Committee noted that the recommended dose of febuxostat is 80 mg



per day, which may be escalated to 120 mg per day if serum urate levels remain below target (0.36 mmol/l) after 2-4 weeks on 80 mg per day.

- 13.9 The Committee reviewed the three key Phase III trial reports provided by the applicant: FACT (Becker et al. NEJM 2005;353:2450-2461), CONFIRMS (Becker et al. Arthritis Res Ther 2010;12:R63) and APEX (Schumaker et al. Arthritis Rheum 2008;59:1540-1548), as well as reports of two open-label extension studies: EXEL (extension to CONFIRMS and APEX, Becker et al. J Rheumatol 2009;36:1273-1282) and FOCUS (extension to a 28-day Phase II study, Schumaker et al. Rheumatology 2009;48:188-194). In summary, the Committee considered that the publications provided good-quality evidence that febuxostat at doses of 80–120 mg/day is effective in achieving the target serum urate level <0.36 mmol/l, and is more effective than allopurinol at doses up to 300 mg per day in achieving this target.
- 13.10 The Committee noted that the reduction in tophi was similar for febuxostat and allopurinol (300 mg). The FACT (Becker et al. NEJM 2005;353:245-261) trial reported no statistically significant differences in the percentage of tophus area or in the reduction in the number of tophi, when febuxostat was compared with allopurinol (300 mg).
- 13.11 However, the Committee noted that febuxostat did not appear to be more effective than allopurinol (at doses up to 300 mg per day) in reducing the frequency of gout flares after up to 12 months of treatment. Members noted that in the FACT study more gout attacks were reported in patients on febuxostat 120 mg per day in the first eight weeks compared with allopurinol 300 mg per day (36% vs 31% p<0.001). Similar rates of gout attacks were reported in patients taking febuxostat 80 mg and allopurinol 300 mg, and similar rates were observed in all treatment arms after eight weeks.
- 13.12 The Committee noted that there appeared to be no evidence that febuxostat is as effective as, or more effective than, allopurinol at doses greater than 300 mg per day, noting that current best practice was to use doses of allopurinol greater than 300 mg per day where tolerated if the target serum urate level was not achieved with lower doses. The Committee noted that there was also no evidence provided in support of febuxostat efficacy or tolerability in patients who had received inadequate benefit from, or were intolerant to, allopurinol, or comparing the effectiveness of febuxostat with probenecid or benzbromarone. The Committee noted that there were ongoing studies of febuxostat versus higher doses of allopurinol.
- 13.13 The Committee considered that febuxostat was generally well tolerated, but noted that concerns have been raised by the US Food and Drug Administration about the potential for febuxostat to cause cardiovascular adverse events, and other reports suggesting liver dysfunction and skin reactions. The Committee noted that there was a lack of long-term safety data for febuxostat.
- 13.14 The Committee considered that febuxostat may be easier to use than allopurinol in patients with renal impairment because, unlike allopurinol, dose titration is not necessary in this patient group.
- 13.15 The Committee considered that, given the substantially higher price of febuxostat compared to allopurinol, dose escalation of allopurinol (where tolerated) would be a

more cost-effective means of reducing serum urate levels in treatment-resistant patients, including in patients with renal impairment.

- 13.16 The Committee considered that there was insufficient evidence of benefit of febuxostat versus the alternative funded options to justify a significant price premium for febuxostat. The Committee considered that there may be a place for febuxostat in patients who were intolerant to allopurinol at doses required to achieve therapeutic effect; however, given that febuxostat was also considerably more expensive than probenecid and benzbromarone it would be reasonable to place restrictions on its use such that a trial of probenecid would be required prior to febuxostat and that access criteria for febuxostat would be no less restrictive than benzbromarone.
- 13.17 The Committee noted that, given the different mechanisms of action, it is possible that patients would take both febuxostat and benzbromarone if both were funded, and that this should be taken into account in economic evaluation.

## 14 Topical anaesthetics

### Application

- 14.1 The Committee reviewed a request from PHARMAC staff for advice on whether a wider range of topical anaesthetics should be funded on the Pharmaceutical Schedule.

### Recommendations

- 14.2 The Committee **recommended** that benzocaine gel 20% and amethocaine (tetracaine) gel 4% be listed in Section H of the Pharmaceutical Schedule (i.e. to be included in the Hospital Medicines List);
- 14.3 The Committee **recommended** that amethocaine (tetracaine) gel 4% be listed in Section B of the Pharmaceutical Schedule, and that it should be available on a PSO, with a high priority; and
- 14.4 The Committee **recommended** that the Special Authority criteria for EMLA cream be widened in the Pharmaceutical Schedule to include its use in “painful procedures” and to remove the age restriction, with a high priority.
- 14.5 The Decision Criteria particularly relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand;; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals.*

### Discussion

- 14.6 The Committee noted that the areas of use for topical anaesthetics are potentially wide-ranging. Members noted that the literature suggests that topical anaesthetics are often used during dressing changes in patients with chronic wounds (e.g. to alleviate pain during debridement), in alleviating the pain associated with post herpetic neuralgia

(PHN), and also for relief of post-partum perineal pain whilst receiving inpatient hospital care and following discharge from hospital. Members noted that topical anaesthetics are also used in the paediatric setting as they can be applied painlessly without needles and may reduce the need for physical and chemical restraints during paediatric procedures prior to intramuscular injections, venepuncture, uncomplicated facial or scalp lacerations before suturing.

- 14.7 The Committee considered the evidence for topical anaesthetic in dressing changes. The Committee noted that there appeared to be no evidence supporting the use of lignocaine 2% gel in the context of wound dressing changes. Members noted, however that there are numerous studies which consider Eutectic Mixture of Local Anaesthetics (EMLA) in this setting. The Committee noted a recent Cochrane review (Briggs et al. Cochrane Database Syst Rev 2012;11:CD001177) which concluded that EMLA appears to provide effective pain relief during the debridement of venous leg ulcers.
- 14.8 The Committee noted a review of 13 clinical investigations of EMLA cream for sharp leg ulcer debridement by Vanscheidt et al. (Eur J Dermatol 2001;11:90-96). The review reported that EMLA applied to the ulcer for 30–45 minutes under occlusion significantly reduced the pain from sharp debridement, decreased the incidence of post-debridement pain and reduced the time needed to achieve a clean ulcer.
- 14.9 The Committee considered the evidence for topical anaesthetics currently available in New Zealand for post herpetic neuralgia. The Committee noted a review by Khaliq et al (Cochrane Database Syst Rev 2007;(2):CD004846) which examined the efficacy and safety of topical lignocaine in the treatment of postherpetic neuralgia. The Committee noted that the reviewer concluded that there was insufficient evidence to recommend topical lignocaine as a first-line agent in the treatment of post herpetic neuralgia with allodynia. The Committee noted that International Association for the Study of Pain (IASP) and the European Federation of Neurological Studies (EFNS) guidelines both recommend lignocaine 5% patches as first-line treatment for post-herpetic neuralgia; however, this formulation is not currently available in New Zealand.
- 14.10 The Committee considered the evidence for topically applied anaesthetics for treating perineal pain after childbirth. The Committee noted a review by Hedayati et al. (Cochrane Database Syst Rev 2005;(2):CD004223) which concluded that evidence for the effectiveness of topically applied local anaesthetics for treating perineal pain is not compelling and stated that there has been no evaluation for the long-term effects of topically applied anaesthetics for treating perineal pain after childbirth.
- 14.11 The Committee considered the evidence for the use of topical anaesthetics for minor skin lacerations. The Committee noted a short review by Ferguson (Emerg Med J 2005;22:507-509), which concluded that topical anaesthetics should be used for selected minor lacerations in children as they have similar efficacy to lignocaine infiltration but are less painful to apply. Members noted that the review stated that the ideal combination and concentration of agents providing optimal levels of efficacy and safety is yet to be decided.
- 14.12 The Committee considered the evidence for topical anaesthetics for the reduction of children's pain associated with needle insertion. The Committee noted a review by Lander et al (Cochrane Database Syst Rev 2006;(3):CD004236) which reviewed

randomised controlled trials that compared EMLA and amethocaine (tetracaine) for relieving children's pain from intravenous (iv) cannulation or venepuncture. The review concluded that for anaesthetic efficacy, amethocaine significantly reduced the risk of pain compared to EMLA when all pain data were combined into a common pain metric. The Committee noted that the reviewers concluded that although EMLA is an effective topical anaesthetic for children, amethocaine is superior in preventing pain associated with needle procedures.

- 14.13 The Committee considered the evidence for topical anaesthetics in dental procedures. Members noted that authors of a review of topical anaesthetic agents and techniques by Meechan et al. (Dent Clin North Am 2002;46:759-766) stated that when used as a single agent, lignocaine is effective at concentrations between 5% and 20% and that there is evidence of a dose response with topical lignocaine. Members noted that the study authors also stated that benzocaine is effective when used alone at a concentration of 20% and when combined at a dose of 15% with 1.7% amethocaine. The Committee noted that hospital dentists currently use topical benzocaine 20% and amethocaine gel 2% in paediatric dentistry and considered that it would be important for these products to continue to be available in hospitals for this use.
- 14.14 Members noted that district/community health nurses changing dressings in the community do not have access to pre-dressing analgesic medications. The Committee speculated that if these medications were available, they might be applied under occlusion prior to wound debridement, which could potentially lead to more aggressive debridement of ulcers and risk of complications. The Committee considered that this possibility should be discussed with the Dermatology Subcommittee prior to any decision to widen access to topical anaesthetics for this use.
- 14.15 Members noted that there is a very small risk of methaemoglobinaemia, particularly from benzocaine and prilocaine, and that there was a possibility of lignocaine toxicity if a topical presentation was applied to very large areas of skin for prolonged periods of time.
- 14.16 The Committee considered that the paediatric population undergoing painful procedures like venepuncture, iv cannulation and patients with chronic venous leg ulcers requiring debridement would benefit from local anaesthetics.
- 14.17 The Committee noted that there was a disparity between the availability of topical anaesthetics for children undergoing venepuncture or iv cannulation in the community compared with hospital emergency departments, which is a particular issue for rural general practice. The Committee also noted that there was an age disparity for EMLA in that it is only currently funded for children (subject to Special Authority restrictions).
- 14.18 On balance, the Committee considered that the best available evidence for topical anaesthetics for community use was for amethocaine gel 4% and for EMLA.
- 14.19 The Committee considered that it was difficult to estimate the financial impact of listing amethocaine gel 4% and/or widening access to EMLA but it would likely be high as there was potential for these presentations to be used widely in a large range of conditions, including situations not considered by the Committee such as insect bites, severe sunburn etc. However, the Committee considered that these were important

pain relief options that should be available to patients. Members noted, for example, that even one painful procedure in a child can have long-term detrimental psychological effects.

- 14.20 The Committee noted that there were other potentially useful topical anaesthetic preparations that PHARMAC should investigate, such as lidocaine with adrenaline and tetracaine gel and lignocaine patches 5%.

## **15 Nilotinib for chronic myeloid leukaemia - 2nd/3rd line**

### **Application**

- 15.1 The Committee considered an application from the Haematology Society of Australia and New Zealand (HSANZ) for the listing of nilotinib (Tasigna) on the Pharmaceutical Schedule for the treatment of 3 groups of patients with Chronic Myeloid Leukaemia (CML):
- 15.1.1 patients who have failed, or are intolerant to both imatinib and dasatinib treatment; and
  - 15.1.2 patients with high risk disease who have failed first line dasatinib; and
  - 15.1.3 patients who have failed first line imatinib treatment with mutations that predict better response to nilotinib rather than dasatinib.

### **Recommendation**

- 15.2 The Committee recommended that this funding application for nilotinib in the Pharmaceutical Schedule be declined. The Committee considered that patients who require nilotinib in these settings would be best managed through the Named Patient Pharmaceutical Assessment (NPPA) scheme.
- 15.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

### **Discussion**

- 15.4 The Committee noted it had reviewed nilotinib previously on a number of occasions, but that this was the first time it had considered this set of access criteria. It was noted that CaTSOP had reviewed this application at its November 2012 meeting and recommended it for funding with a high priority.
- 15.5 Members noted that when imatinib was introduced it revolutionised the treatment of CML (imatinib has been publically funded in New Zealand since 2002). Since then

second and third generation treatments have been developed (dasatinib, a second generation treatment, has been funded since 2009). Generic entry of imatinib is expected in the near future along with the associated price reductions. It was noted that nilotinib is currently more expensive than currently funded treatments.

- 15.6 When considering the number of patients that may be eligible for nilotinib under the proposed criteria, PTAC considered the following: six year follow-up data of imatinib in the IRIS trial (Hochhaus et al. *Leukemia* 2009;23:1054-1061), NICE assessment of imatinib, nilotinib and dasatinib (NICE technology appraisal 241, 2012), retrospective analysis of resistance to imatinib (Iqbal et al. *PLoS ONE* 2013;8(2):e55717), retrospective analysis of nilotinib and dasatinib (Griffin et al. *Curr Med Res Opin* 2013;29:623-631), and the New Zealand experience. Members recommended using NICE's estimate of 40% of patients developing resistance or intolerance to first-line treatment. When estimating the number of patients taking a 3rd agent, members agreed this figure could be applied to the second line population as well, i.e. approximately 40% of second-line patients would become eligible for a third line agent.
- 15.7 The Committee noted that nilotinib has been shown to have more extensive and faster responses than imatinib when used in treatment naïve patients (Kantarjian et al. *Lancet Oncol* 2011;9:841-851). Members however considered that this evidence did not directly relate to the application as the application was for patients who have tried dasatinib and in some cases imatinib.
- 15.8 The Committee agreed that nilotinib had the same or similar effect as dasatinib in both the first and second-line settings. A report from NICE arrived at the same conclusion (Rodgers et al. *Health Technol Assess* 2012;16(22):1-410). It was noted there is a lack of direct comparison studies between nilotinib and dasatinib.
- 15.9 The Committee considered evidence for nilotinib following imatinib treatment (Kantarjian et al. *Blood* 2011;17(4):1141-1145; Le Coutre et al. *Leukemia* 2012;(6):1189-1194; Giles et al. *Leukemia* 2012;1:107-112; Nicolini et al. *Cancer* 2012;118(1):118-126; Rodgers et al. *Health Technol Assess* 2012;16(22); Griffin et al. *Curr Med Res Opin* 2013;6:623-631). It was considered that nilotinib has similar efficacy in patients who are resistant or intolerant to imatinib. PTAC noted the lack of randomised controlled trials and that the evidence was confined to single arm observational studies. Members noted the evidence for nilotinib (and dasatinib) remains immature and is confined to surrogate end-points.
- 15.10 The Committee considered there is very limited evidence for the efficacy of nilotinib when refractory or intolerant to both imatinib and dasatinib.
- 15.11 The Committee considered the evidence for the treatment of high risk patients of using dasatinib as a first line agent and then using nilotinib. Members noted that patients were classified as high risk using prediction scores. The EUROS prediction score system was developed based on data from 2060 patients from studies of imatinib treatment (Hasford et al. *Blood* 2011). The score was used to determine the surrogate end-point of complete cytogenetic response at 18 months of treatment. The EUROS has been reported to perform poorly in predicting different rates of overall survival, progression free survival and major molecular response between high and low risk groups (Marin et al. *J Clin Oncol* 2011; Jabbour et al. *Blood* 2012).

- 15.12 The Committee considered the evidence of treating patients following imatinib failure with nilotinib rather than dasatinib, based on tumour mutation. Members noted that US and European guidance (ELN and NCCN) on monitoring for CML patients recommend mutation analysis in instances of inadequate imatinib response and suggest that mutation screening may assist in the choice of second line agents. However, clear guidance is not provided, apart from with T315I, as predictive values have not been consistently shown (T315I mutation is resistant to both nilotinib and dasatinib and thus its presence favours neither treatment).
- 15.13 The Committee considered a retrospective study that assessed dasatinib efficacy in patients with CML following imatinib treatment (Muller et al. Blood 2009). There were 63 different BCR-ABL mutations. After 2 years of follow-up, dasatinib treatment of imatinib-resistant patients with or without a mutation reportedly resulted in similar response rates (complete cytogenetic response: 43% vs. 47%). Apart from T315I there was little difference in time to major response. While mutations at Q252H, F317L and E355G were suggestive of decreased complete cytogenetic response, no appropriate comparative data were provided. PTAC concluded that there does not appear to be a clear consensus on management of these patients.
- 15.14 Given that both imatinib and dasatinib are fully funded and the lack of strong evidence favouring the benefits of nilotinib as third line treatment or the use of nilotinib instead of imatinib/dasatinib due to the presence of mutations, the Committee considered that patients who require nilotinib in these settings would be best managed through the Named Patient Pharmaceutical Assessment (NPPA) scheme at this time.
- 15.15 PTAC considered that there would be a significant fiscal risk with making nilotinib available for patients who were intolerant of imatinib and dasatinib, given the subjective nature of this criterion. The Committee therefore considered that it would be more appropriate to assess these patients on a case-by-case basis through the NPPA scheme.
- 15.16 PTAC noted that the evidence of treatment choices based on tumour mutation is emerging. The Committee noted that it should review its recommendation if significant positive evidence in this area emerges.

## **16 Vemurafenib for melanoma, stage IIIc/IV with BRAF V600 mutation**

### **Application**

- 16.1 The Committee reviewed an application from Roche New Zealand for the funding of vemurafenib for treatment of patients with unresectable stage IIIc or IV melanoma positive for the BRAF V600 mutation.

### **Recommendation**

- 16.2 The Committee **recommended** that funding for vemurafenib in this indication should be declined.

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

## Discussion

- 16.4 The Committee noted that it and CaTSoP had already seen a funding application for vemurafenib for this indication in February 2012. PTAC had recommended that funding for vemurafenib should be declined, even after CaTSoP had recommended that vemurafenib should be listed with a low priority. It was noted that the reason for the recommendation for declining the funding was due to high costs and limited clinical benefits. The current application included updated clinical information, a reworked cost utility analysis and an updated price.
- 16.5 The Committee noted evidence from the BRIM3 study (Chapman et al. NEJM 2011;364:2507-2516) which compared vemurafenib with dacarbazine. It was noted that this evidence had been considered previously by the Committee and one of the Committee's concerns had been that the data was based on a short median duration of follow-up.
- 16.6 The Committee noted evidence from a slide presentation at the 2012 American Society of Clinical Oncology annual meeting, which contained updated data from the BRIM3 trial with a median follow-up of 11.4 months. Overall, the Committee considered that these unpublished data suggested that vemurafenib had better efficacy than dacarbazine. The Committee considered that the updated data gave greater precision for survival with vemurafenib compared with dacarbazine, but did not significantly change the health benefits attributed to vemurafenib previously considered by the Committee. The updated data reported median overall survival censored at crossover of 13.6 months for vemurafenib versus 9.7 months for dacarbazine and at 6 months a 30% risk reduction of death. Median progression free survival was 6.9 months and 1.6 months for vemurafenib and dacarbazine respectively. Tumour responses were better with vemurafenib, with tumour response rates of 57% for vemurafenib compared with 8.6% for dacarbazine.
- 16.7 The safety data reported for BRIM3 (Chapman et al. NEJM 2011;364:2507-2516) indicated 18% of patients on vemurafenib developed keratoacanthoma or cutaneous squamous cell carcinoma of the skin (or both). In addition, the updated data showed that 2.4% of patients in the vemurafenib group developed new primary melanomas.
- 16.8 The Committee noted that the survival curves (for both the censored and non-censored at crossover sets) displayed convergence, which may imply that vemurafenib's effects may be temporary. The Committee considered that there was no evidence available for long-term cures or survival, as the long-term data applied to a sole patient who had survived 24 months by the data cut-off.
- 16.9 The Committee noted the contents of the health economic analysis submitted by the supplier. The utility gains in the supplier model derived from assumptions of prolonged



progression free survival and longer time in the progressed disease state. The supplier analysis did not model a quality of life difference on vemurafenib versus dacarbazine, and the Committee agreed that there was no evidence to suggest this. Overall survival was determined using the 'rank preserving structural failure time model' which is a theoretical model to attempt to remove the effect of crossover. Members considered that the survival times modelled were overly optimistic.

- 16.10 The Committee noted that the submission assumes a positive testing rate for the BRAF V600 mutation of 28%, based on 90 (25 positive) tests carried out in New Zealand by Roche. The BRIM3 publication (Chapman et al. NEJM 2011;364:2507-2516) reported rates to be 40-60%. The Committee considered that the mutation prevalence would have little effect on cost effectiveness, but would have a large budget impact and there is still a possibility that it could be as high as 40-60% in New Zealand. Members noted that funding vemurafenib would have additional costs associated with monitoring and treating new skin lesions, and additional CT scans for monitoring the effect of vemurafenib.
- 16.11 The Committee considered that there were few funded alternatives available and that vemurafenib improved the treatment of melanoma in this setting. Overall, the Committee considered that it would maintain its previous recommendation, that this application for vemurafenib should be declined because it only provided only a small benefit for a very high cost.