

## **PTAC meeting held on 14 &15 August 2014**

**(minutes for web publishing)**

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

PTAC may:

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

**Record of the  
Pharmacology and Therapeutics Advisory  
Committee Meeting  
Held on 14 & 15 August 2014**

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## 1. Acetretin and Isotretinoin

- 1.1. PTAC considered its previous minute of 8 and 9 May 2014 regarding acitretin and isotretinoin. Members noted that the inconsistent use of prescriber type definitions for both products in the minutes. Members considered that the intent of the discussion had been to ensure that prescribers were aware of the risks of teratogenicity of retinoids as there was no central oversight in New Zealand unlike other international countries.
- 1.2. Members considered that it would be appropriate to require medical practitioners to be vocationally registered or Nurse Practitioners to be working in a relevant scope of practice to apply for a pharmaceutical by Special Authority.
- 1.3. The Committee **recommended** that the Special Authorities for acitretin and isotretinoin be amended to require applicants to be either vocationally registered medical practitioners or Nurse practitioners working in a relevant scope of practice throughout.

## 2. Correspondence/Matters Arising

### Cetuximab/bevacizumab

- 2.1. Correspondence regarding cetuximab (Erbix) and bevacizumab (Avastin) for metastatic colorectal cancer confined to the liver.
  - 2.1.1. The Committee considered correspondence from Merck, Serono and Roche Products NZ limited regarding a recently published study of cetuximab in patients with KRAS exon 2 wild-type resectable or suboptimally resectable colorectal liver metastases (Primrose et al Lancet Oncology, 2014, 15, 601-11).
  - 2.1.2. The Committee noted that based primarily on positive evidence from a study by Ye et al (J Clinical Oncology 2013; 31:1931-38) CaTSOP had previously recommended that cetuximab be funded for neoadjuvant treatment of patients with K-RAS wild-type metastatic colorectal cancer (mCRC) whose metastases are limited to the liver. However, the Committee noted that in the new study from the Primrose et al, which was not considered by CaTSOP, the addition of cetuximab to chemotherapy and surgery resulted in shorter progression-free survival. Members considered that the Primrose and Ye studies enrolled similar patients and because these two studies had different results there remained doubt about the benefit of cetuximab treatment. Members noted that the other RAS mutations had recently been identified that conferred resistance to cetuximab and considered further evidence was needed to clarify the patient group(s) that would benefit from cetuximab treatment.
  - 2.1.3. The Committee **recommended** that the application to fund cetuximab in combination with irinotecan-based chemotherapy for the first line neoadjuvant treatment of patients with K-RAS wild-type metastatic colorectal cancer (mCRC) whose metastases are limited to the liver be declined.
  - 2.1.4. The Committee also noted new evidence provided by Roche including an unpublished study comparing cetuximab with bevacizumab (CALGB-80405) in the first line treatment of K-RAS wild-type metastatic colorectal cancer (mCRC) and published studies of bevacizumab in unresectable mCRC confined to the liver. Members also noted a revised commercial proposal from Roche.
  - 2.1.5. The Committee restated its previous low-priority **recommendation** 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, with funding limited for a maximum of 4 treatment cycles.

### **Pertuzumab**

2.2. Correspondence regarding pertuzumab (Perjeta) for patients with HER 2 positive breast cancer

2.2.1. The Committee noted correspondence from Roche Products NZ limited regarding its February 2013 minute for funding of pertuzumab (Perjeta).

2.2.2. The Committee considered that no new evidence had been provided that would change its previous view and reiterated its February 2014 **recommendation** that pertuzumab should be funded when used in combination with trastuzumab for the first line treatment of patients with HER2-positive metastatic breast cancer with low priority.

### **Ipilimumab**

2.3. Correspondence regarding ipilimumab (Yervoy) for patients with metastatic melanoma.

2.3.1. The Committee noted correspondence from Bristol-Myers Squibb (NZ) Limited regarding its February 2014 minute and recommendations for ipilimumab (Yervoy) on the Pharmaceutical Schedule for the treatment of patients with previously treated unresectable Stage IIIc or IV melanoma.

2.3.2. The Committee noted that BMS had indicated longer term follow-up overall survival data from the pivotal randomised study previously published by Hodi et al. (N Eng J Med 2010;363):711-23) was not available.

2.3.3. The Committee reiterated its previous **recommendation** that the application be declined.

## **3. Rituximab for Chronic Lymphocytic Leukaemia**

### **Application**

3.1. The Committee considered an application from a clinician requesting that rituximab retreatment be funded for patients with chemosensitive relapsed chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), which has responded for at least 24 months to prior combination fludarabine, cyclophosphamide, rituximab (FCR) treatment.

### **Recommendation**

3.2. The Committee considered that there was insufficient evidence to support the funding of rituximab retreatment in patients with relapsed/refractory CLL or SLL and **recommended** that the application be declined.

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

## Discussion

- 3.4. The Committee noted that in 2010 and 2011 it, and its Cancer treatments Subcommittee (CaTSoP), had considered an application from Roche Products (NZ) Ltd for the funding of rituximab for treatment naive and relapsed refractory CLL. The Committee noted that it had recommended that rituximab be funded for treatment of naive CLL patients and relapsed refractory, rituximab-naive CLL patients but that rituximab retreatment be declined. The Committee considered at that time that there was no evidence provided to support the use of rituximab retreatment in patients with CLL disease.
- 3.5. The Committee noted that no new evidence was provided in support of the application. Members noted that two studies remained the primary evidence for rituximab in patients with CLL; the REACH study (Robak et al. J Clin Oncol. 2010;28(10):1756-65) and the Wierda et al study (J Clin Oncol. 2005;23(18):4070-8), both of which had previously been considered by PTAC and CaTSoP.
- 3.6. The Committee noted that the REACH study excluded patients who had previously received rituximab treatment (i.e. it comprised rituximab naive patients alone) so was not relevant to the application. Members noted that whilst 12% (21) of the patients enrolled in the Wierda study had previously received rituximab, no subgroup analysis of outcomes in this group was performed, so it was not possible to determine the benefit and risks of rituximab retreatment in patients with CLL.
- 3.7. The Committee noted that the applicant had provided a Cochrane group meta-analysis (Bauer et al, Cochrane Database of Systematic Reviews 2012, Issue 11); however members noted that this did not specifically address the topic of rituximab retreatment. Members noted that both the National Comprehensive Cancer Network guidelines and European Society for Medical Oncology guidelines recommended that in patients with relapsed refractory CLL, first line treatment including rituximab should be repeated; however members noted that these recommendations were based on evidence from the Wierda and REACH studies.
- 3.8. The Committee considered that evidence from follicular lymphoma studies suggested that rituximab retreatment/maintenance treatment was plausible; however, members noted that there was no evidence in CLL and that rituximab remained a relatively expensive treatment. Members acknowledged it was unlikely there would any clinical trials in CLL because overseas treatment guidelines currently recommended rituximab retreatment as standard care.
- 3.9. The Committee acknowledged there was similar paucity of evidence for some currently funded uses of rituximab such as treatment of lymphoplasmacytic lymphomas, however, members noted that these were rarer diseases and had been funded as a result of historic use in DHB hospitals and the Committee had not specifically reviewed evidence in these settings.

## 4. Sofosbuvir (Sovaldi) for the treatment of hepatitis C

### Application

- 4.1. PHARMAC has received an application from Gilead Sciences for the listing of sofosbuvir in the Pharmaceutical Schedule for the treatment of Hepatitis C infection.

### Recommendation

- 4.2. The Committee **recommended** listing sofosbuvir for the treatment of hepatitis C infected patients, non-genotype 1, who were on the liver transplant list with a high priority.

- 4.3. The Committee **recommended** listing sofosbuvir for the treatment of hepatitis C infected patients with a low priority.
- 4.4. The Committee **recommended** PHARMAC seek the advice of the Anti-Infective Subcommittee and Gastroenterology Subcommittees as to any further hepatitis C infected subpopulations that were a high priority for sofosbuvir compared to currently available treatments.
- 4.5. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

## Discussion

- 4.6. The Committee noted that the application was poorly organised which impeded the review process. Members considered that applications should include all published reports of trials, including the relevant supplements to published main manuscripts, and preferably paginate the application. Members considered that it would have been helpful to report sub-groups who could benefit the most and possible funding approaches to mitigate the very high budget impact.
- 4.7. Members noted that the currently funded treatments for hepatitis C virus (HCV) were pegylated interferon and ribavirin, and, for HCV genotype 1 with IL-28 CT and TT alleles, boceprevir in combination with these treatments. Members noted that current treatment of boceprevir in combination with pegylated interferon and ribavirin achieved a Sustained Virological Response at 12 weeks post-treatment (SVR-12), of 67% in HCV genotype 1. Members noted that pegylated interferon and ribavirin achieved a SVR-12 in 82% of patients with HCV genotype 2 or 3. The committee noted that SVR-12 can be interpreted as eradication of HCV.
- 4.8. The Committee noted that sofosbuvir was an inhibitor of the hepatitis C NS5B RNA polymerase and is the first registered agent for this. Members noted that sofosbuvir was registered for use in combination with ribavirin or pegylated interferon and ribavirin for all HCV genotypes. The Committee noted that no randomised controlled trials (RCTs) of sofosbuvir compared against the currently funded treatment regimens were provided.
- 4.9. The Committee noted one systematic review of all RCTs and cohort studies of sofosbuvir in combination with other medication, Liu et al (International Journal of Antimicrobial Agents 2014, 44: 145-51). The review included a meta-analysis of proportion of patients responding and having adverse effects. Members noted the review included 14 studies of sofosbuvir in combination with pegylated interferon and ribavirin (triple therapy) in treatment naive HCV patients (all genotypes) who achieved a SVR-12 of 89% (95% CI 85-92%). Members noted that 87% (95% CI 82-91%) of treatment naive genotype 1 patients achieved an SVR-12 using triple therapy compared with 73% (95% CI 56-86%) of patients using sofosbuvir with ribavirin. The Committee noted that there was no data for treatment experienced genotype 1 patients. Members noted that 94% (95% CI 85-98%) of treatment naive genotype 2/3 patients using triple therapy achieved an SVR-12 compared with 81% (95% CI 34-97%) of patients using sofosbuvir with ribavirin. Members noted that 62% (95%CI 38-81%) of treatment experienced genotype 2/3 patients using sofosbuvir with ribavirin achieved an SVR-12.
- 4.10. The Committee considered the evidence for genotype 1 treatment naive patients to be of good quality and moderate strength. Members noted that the key information was two RCTs, Lawitz et al (Lancet Infect Dis 2013 13: 401-8) and Kowdely et al (Lancet 2013; 381:2100-7) and one cohort study Lawitz et al (N Engl J Med 2013; 368:1878-87).

Members noted that the evidence gave an estimate of SVR-12 in the genotype 1 treatment naive population of approximately 90% for patients treated with 12 weeks of triple therapy.

- 4.11. The Committee considered the evidence for genotype 2 treatment naive patients to be of good quality and moderate strength. Members noted that the key information was two RCTs, Jacobson et al (N Engl J Med 2013; 368:1867-77) and Lawitz et al (N Engl J Med 2013; 368:1878-1887) and one cohort study Zeumzem et al (N Engl J Med 2014; 370:1993-2001). Members noted that the evidence gave an estimate of a SVR-12 in the genotype 2 treatment naive population of between 93% and 97% for patients treated with 12 weeks of sofosbuvir and ribavirin. Members noted that this SVR 12 rate was higher than the meta-analysis which did not differentiate between genotype 2 and 3.
- 4.12. The Committee considered the evidence for genotype 3 treatment naive patients to be of good quality and moderate strength. Members noted that the key information was two RCTs, Jacobson et al (N Engl J Med 2013; 368:1867-77) and Lawitz et al (N Engl J Med 2013; 13: 401-8) and one cohort study Zeumzem et al (N Engl J Med 2014; 370:1993-2001). Members noted that the evidence gave an estimate of a SVR-12 in the genotype 2 treatment naive population of between 27% and 61% for patients treated with 12 weeks of sofosbuvir and ribavirin. Members noted that cohort study also provided a 24 week sofosbuvir and ribavirin treatment arm which resulted in a SVR-12 of 94%.
- 4.13. The Committee noted that there was no evidence provided for use of sofosbuvir for genotype 1 treatment experienced patients.
- 4.14. The Committee considered the evidence for genotype 2 treatment experienced patients to be of moderate quality and moderate strength. Members noted that the key information was one RCT, Jacobson et al (N Engl J Med 2013; 368:1867-77) and two cohort studies Zeumzem et al (N Engl J Med 2014; 370:1993-2001) and Lawitz et al (AASLD 2013 Abstract). Members noted that the evidence gave an estimate of a SVR-12 in the genotype 2 treatment experienced population of between 86 and 96% for patients treated with 12 weeks of sofosbuvir and ribavirin and in one cohort study 12 weeks of sofosbuvir, ribavirin and pegylated interferon. Members noted one RCT from Jacobson et al (N Engl J Med 2013; 368:1867-77) which used a 16 week sofosbuvir and ribavirin treatment arm which resulted in a SVR-12 of 94%.
- 4.15. The Committee considered the evidence for genotype 3 treatment experienced patients to be of moderate quality and moderate strength. Members noted that the key information was one RCT, Jacobson et al (N Engl J Med 2013; 368:1867-77) and two cohort studies Zeumzem et al (N Engl J Med 2014; 370:1993-2001) and Lawitz et al (AASLD 2013 Abstract). Members noted that there were various treatment lengths in the trials. Members noted that 24 weeks of sofosbuvir and ribavirin achieved an SVR-12 of 79% and a 12 week course of triple therapy resulted in an SVR-12 of 83%.
- 4.16. The Committee considered that the supplier estimates of patient distribution by genotype were appropriate as they had been sourced from Professor Ed Gane. The Committee considered that, based on Thein et al (Hepatology 2008;48:418-431) genotype 1 would progress more slowly to cirrhosis than other patients. Members noted the paper by Probst et al (J of Viral Hepatitis 2011; 18: 745-759) which suggested HCV genotype 3 had a higher rate of progression to cirrhosis with an odds ratio for progression compared to other genotypes of 1.52 (85% CI 1.12 to 2.07).
- 4.17. The Committee noted that there was no evidence of an increase in prevalence of HCV in Māori or Pacific People.
- 4.18. The Committee noted that the applicant included in their model a quality of life improvement from achieving SVR-12, regardless of any other change in disease state of 0.05. The Committee noted Stepanova et al (Alimentary Pharmacology and Therapeutics 2014) which reports that, in the FUSION study, SVR was associated with an SF-6D-

derived health utility improvement of 0.026 and an EQ-5D-derived utility improvement of 0.043. The Committee also noted Hsu et al (J Gastro Hepatol 2011; 27:149-157) and Wright et al (Health Technol Assess 2006;10(21):1-113) which support the premise of a health gain from SVR-12. The Committee considered that a maximum utility gain from SVR of between 0.026 and 0.043 would be reasonable as they were directly derived from randomised controlled trials of sofosbuvir.

- 4.19. The Committee considered that sofosbuvir would be most beneficial to those patients with HCV who had hepatic fibrosis or cirrhosis. Members also considered that sofosbuvir would also benefit non-genotype 1 HCV patients who had not achieved SVR-12 with current therapy. Members noted some populations may be at greater risk of progression to cirrhosis and may benefit from sofosbuvir access including co-infection with HIV or hepatitis B, alcoholics, diabetes and obesity. Members also noted that patients with HCV awaiting liver transplantation would benefit from treatment.
- 4.20. The Committee considered that sofosbuvir was a clinically effective drug. Members considered there would be significant fiscal risk with listing sofosbuvir, and considered that currently it should be restricted to those whose clinical condition required immediate treatment, particularly as members noted that there were a significant number of oral agents in development for the treatment of HCV, which were likely to be interferon free. Members considered that HCV typically progressed slowly and that patients could wait until future treatments were available, which may be more effective, have less adverse effects, or the issues of fiscal risk for more widespread use of this agent, or new agents, was resolved.
- 4.21. The Committee anticipated that the new oral agents, associated with interferon free regimes, would be available in the next 3 to 5 years.
- 4.22. The Committee noted that although it could be argued that eradication of HCV by widespread use of an agent such as sofosbuvir might reduce transmission of this illness within New Zealand this would not actually happen unless there was a global eradication scheme. Members noted that HCV was transmitted more easily than HIV from high risk situations, i.e. intra-venous drug use. Members considered that re-infection following eradication would be likely in people undertaking high risk activities. The Committee therefore considered that only individual benefit of treatment should be considered in the cost utility assessment at this time.
- 4.23. Members noted that in the health care setting the estimated risk for infection after a needle-stick or cut exposure to HCV-infected blood is approximately six times greater than the risk for HIV. Members noted that there is a low vertical transmission rate in pregnancy with approximately 7% of children being infected, although this rate was higher in HIV co-infection.
- 4.24. The Committee considered that, at present, HCV non-genotype 1 patients with cirrhosis who were awaiting transplant could not delay treatment because of the risk of reinfection in the transplanted organ in the setting of immunosuppression. This subpopulation was **recommended** for funding of sofosbuvir with a high priority. Members noted that more widespread use of sofosbuvir in other groups creates a large fiscal risk to the pharmaceutical budget. The Committee noted that there may be other HCV subpopulations that might benefit from earlier access to this treatment.
- 4.25. The Committee felt that sofosbuvir was effective for HCV eradication however this needed to be balanced against the high cost of this agent.

## **5. Ingenol mebutate 0.015% for the treatment of facial and scalp solar keratosis**

## Application

- 5.1. The Committee noted the application from Bio CSL for the listing of ingenol mebutate 0.015% in Section B and Part II Section H of the Pharmaceutical Schedule for the indication: treatment of solar (actinic) keratosis lesions on the scalp and face. Members noted that the supplier application is seeking a listing for ingenol mebutate as indicated for the treatment of AKs where other standard treatments are clinically inappropriate or where patients have a history of squamous cell carcinoma (SCC).

## Recommendation

- 5.2. The Committee **recommended** that ingenol mebutate 0.015% be listed in Sections B and H of the Pharmaceutical Schedule for the treatment of actinic keratosis only if cost-neutral to imiquimod cream 5 % at the February 2015 tender price.
- 5.3. 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Governments overall health budget) of any changes to the Pharmaceutical Schedule.*

## Discussion

- 5.4. The Committee noted that facial and scalp actinic keratosis (AK) are pre-malignant and have a transformation rate of 0.25% per year to SCC and SCC induce about 100 deaths per year in New Zealand. Members noted that AK are dynamic and whilst 10-15 % will resolve spontaneously each year, another 10-20 % will develop, particularly in summer. Members considered that there are three main treatment objectives for AK, including prevention, treating individual lesions, and field treatments. Members noted that there is lack of evidence demonstrating that treating AK prevents progression to SCC.
- 5.5. The Committee noted that ingenol mebutate gel is available in two doses - 0.015% for facial and scalp AKs and 0.05% for trunk and limb AKs. Members noted that Australian data indicated the average duration of treatment by Australian dermatologists is 2.98 days. Members further noted that the Australian data indicated the average duration of treatment by Australian GPs was 5.35 days.
- 5.6. The Committee considered that the clinical evidence provided by the applicant for ingenol mebutate was of moderate strength and quality although there have been no head to head comparisons. Members noted that various studies, (sourced outside of the application) for ingenol mebutate and comparator treatments of 5%fluoracil cream (5FU) and 5% imiquimod have mostly been performed on patients with less severe disease on a confined area of skin, usually limited to 25 cm<sup>2</sup>. Members considered that the results of the studies show quite similar response rates: complete response rates 30-50% and good clearance rates 60-80% but that this was dependant on the follow-up period.
- 5.7. The Committee noted results from a Cochrane Review of the relative risk (RR) of complete clearance of AK. Members noted that in this review RR was 8.86 (95% CI: 3.67 to 21.44) for 0.5% 5 FU (3 studies with 522 participants), RR 7.70, (95% CI 4.63 to 12.79) for 5% imiquimod (9 studies with 1871 participants) and RR 4.50, (95% CI: 2.61 to 7.74) for 0.025% to 0.05% ingenol mebutate (2 studies with 456 participants)(Gupta et al, Cochrane Database of Systematic Reviews 2012, 12: CD004415).
- 5.8. The Committee noted that there appeared to be little difference in efficacy between 5 FU, imiquimod and ingenol mebutate. Members considered that compliance will be a key factor in the effective use of these products and that this will be determined by time to response and the adverse effects of each pharmaceutical.

- 5.9. The Committee noted that the time to response was typically 2 weeks for 5 FU, 6 weeks for imiquimod and 2 to 3 days for ingenol mebutate. The Committee noted that the time to response for ingenol mebutate was based on limited experience of use and that this meant it was also difficult to determine the adverse reaction profile. The Committee noted that the key benefit for patients of ingenol mebutate compared to 5-FU and imiquimod was the time to response.
- 5.10. The Committee noted that from 1 February 2015 the Special Authority will be removed from imiquimod cream 5% enabling clinicians to prescribe fully funded imiquimod for the indication of treating AKs. The Committee noted that imiquimod would be the appropriate comparator for ingenol mebutate.

The minute of this item originally approved by PTAC was amended to correct a small number of factual matters at its November 2014 meeting. The version above is the corrected version.

## 6. Zoster virus vaccine

### Application

- 6.1. The Committee reviewed an application from Merck Sharp and Dohme (New Zealand) Ltd for the listing of zoster vaccine on the Pharmaceutical Schedule.

### Recommendation

- 6.2. The Committee **recommended** zoster vaccine be listed on the Pharmaceutical Schedule with a medium priority.
- 6.3. 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; and vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 6.4. The Committee considered that the clinical evidence provided for zoster vaccinated was generally of high quality, although it was noted that evidence for the durability of the vaccine was weak.
- 6.5. The Committee noted that the herpes zoster vaccine in this application is a lyophilized preparation of a live attenuated varicella zoster virus at a dose 14 times greater than that of the varicella (chickenpox vaccine). The Committee noted that the major studies had used a dosage of 0.5 ml compared with the commercial dose of 0.65 ml offered in the application, but noted that the number of plaque forming units per dose is similar between the two with a minimum dosage of 19,400 in the current vaccine versus a dose range between 18,700 and 60,000 in the trials.
- 6.6. The Committee noted that herpes zoster is a common illness in New Zealand. The Committee noted that there was no specific surveillance data available for New Zealand but considered that the data collected in the BEACH study in Australia could be generalised to estimate incidence in New Zealand, giving an incidence of ~13,200 cases of herpes zoster per year for those over 60 year of age (incidence 15.2/1000 for that age group). The Committee noted that apart from the acute illness morbidity, the major consequence of herpes zoster is the development of post herpetic neuralgia (PHN) which occurs in between 5% and 50% of cases and can be very debilitating with only poorly effective treatments for pain relief available.

- 6.7. The Committee noted the Oxman trial (NEJM 2005;352:2271) was a major clinical trial with 38546 participants aged 60 years and older with a mean duration of herpes zoster surveillance of 3.13 years. The primary endpoint in this trial was a burden of illness due to herpes zoster and the secondary endpoint was calculated as the incidence of PHN defined as pain associated with herpes zoster that was rated 3 or more on a scale of 0 to 10, persisting or appearing more than 90 days after the onset of rash. The Committee noted that the use of the zoster vaccine reduced the burden of illness due to herpes zoster by 61%, reduced the incidence of PHN by 67% and reduced the overall incidence of herpes zoster by 51%. There was a marked difference between the 64% efficacy for herpes zoster in the 60-69 year age group compared to the 38% efficacy seen in those aged 70 years and older.
- 6.8. The Committee noted that Schmader et al (Clin Infect Dis.2012;54:922-8) confirmed the efficacy of herpes zoster vaccine with an efficacy of 70% in the 50-59 year age group (95% confidence interval 54.1-80.6%). The study enrolled 22,439 individuals with a mean follow up of 1.3 years.
- 6.9. The Committee noted the retrospective study of individuals enrolled in the Kaiser Permanente Southern California Health Plan conducted by Tseng et al (JAMA 2011;305:160-6). The study matched 75,761 community dwelling vaccinated adults over the age of 60 years 1:3 with 277,283 unvaccinated individuals. Vaccination was associated with a reduced risk of herpes zoster with a vaccine efficacy of 55% consistent across all age strata over a 1.56 year follow-up period.
- 6.10. The Committee noted that, while the efficacy of the vaccine had been clearly demonstrated in the Oxman and Tseng studies, there was uncertainty about the duration of activity extrapolated by the clinical trial data (Schmader et al CID 2012;55:1320). The statistical methodology was considered complex in the extension studies of the Oxman trial and its' add-ons, but there appeared to be some durable activity out to 10 years with a trend towards decreasing vaccine efficacy over time. The Committee considered that cost utility analysis (CUA) modelling would need to be developed with different levels of long-term efficacy within sensitivity analyses.
- 6.11. The Committee noted that further data on the durability of vaccine may arise from case-control studies with longer follow-ups than had been reported for the Kaiser Permanente Southern California Health Plan discussed above.
- 6.12. The Committee noted that shingles and PHN have high levels of morbidity particularly for the elderly and can be life-changing, as some patients do not recover well enough to return to independent living and require rest home care. The Committee noted that acute treatment of zoster is difficult as many patients present late and it is difficult to treat PHN in the elderly as it is difficult to achieve satisfactory pain relief.
- 6.13. The Committee considered that, at current pricing, vaccination against herpes zoster represents a considerable cost to the pharmaceutical budget. The Committee requested PHARMAC prepare CUAs covering a range of assumptions including age-related disease burden scenarios that incorporated remaining life expectancy for specific demographic groups (hence varying need and benefit over time), for PTAC to review. The Committee requested that assumptions include a waning of vaccine efficacy over time as per currently available data, and that sensitivity analysis include a possible booster at 10 years (although members did recognise that the 10-year booster scenario has no current evidence base).

## 7. Teniposide for CNS lymphoma

### Application

- 7.1. The Committee reviewed an application from a clinician for the funding of teniposide for patients with primary central nervous system lymphoma (PCNSL). Members noted that the application had been reviewed by the Cancer Treatments Subcommittee at its March 2014 meeting.

### Recommendation

- 7.2. The Committee agreed with the Cancer Treatments Subcommittee's view and **recommended** that the application to list teniposide on the Pharmaceutical Schedule for the treatment of primary central nervous system lymphoma (PCNSL) be declined. However, the Committee **recommended** teniposide should be funded for individuals enrolled in the HOVON 105 PCNSL/ALLG NHL 24 study.
- 7.3. The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 7.4. The Committee noted that the application was prompted by three NPPA applications for teniposide, all of which were approved. Members noted that teniposide was not registered in New Zealand.
- 7.5. The Committee noted that historically radiation therapy was the exclusive treatment for PCNSL, however, over the last two decades various chemotherapy treatments have been added. Members noted that although not confirmed by a randomised trial, the general consensus is that chemotherapy combined with radiation therapy is superior to radiation alone and this is now the standard approach. However, members noted that treatment is often limited by severe neurotoxicity especially in the elderly.
- 7.6. The Committee noted there was only one randomised controlled study in PCNSL comparing chemotherapy regimens. Members noted that this study (Ferreri AJ et al. Lancet. 2009;374(9700):1512-20) compared high dose methotrexate alone with high dose methotrexate combined with high dose cytosine arabinoside (cytarabine) followed by whole brain radiation in 79 patients. Members noted that the addition of cytarabine resulted in significantly improved 3 year overall survival rates (46% vs 32%).
- 7.7. The Committee noted that in support of the application to fund teniposide for PCNSL the applicant had provided the clinical trial protocol for the HOVON 105 PCNSL/ALLG NHL 24 Phase III trial which was currently enrolling patients in Auckland, Australia and the Netherlands. Members noted that the study compared high dose methotrexate, carmustine ("BiCNU"), teniposide ("Vumon"), and prednisolone (MBVP) chemotherapy with or without rituximab in newly diagnosed PCNSL patients. Members noted that the study planned to enrol 200 patients and had currently enrolled approximately 120 patients with an interim analysis planned for later in 2014.
- 7.8. The Committee noted that the use of MBVP in HOVON study is based on a single arm study in 52 patients with PCNSL (Poortmans et al J Clin Oncol 2003;21:4483-8) and considered that the strength and quality of this evidence to be low. Members noted that this regimen achieved a complete response in 69% of patients and a partial response in 11%, with two and three year survival estimates of 69% and 58% respectively. However,

members noted that the toxicity of the regimen was very high with grade three and four toxicities relating to haematology parameters, infection, neurotoxicity, genitourinary, liver and allergy being recorded and the death of five patients was attributed to treatment related causes.

- 7.9. The Committee noted that cognitive function and quality of life data from this study were reported separately (Harder et al. Neurology 2004;62:544-55); members noted that additional criteria applied to the patients included in the QoL study, including patients must be at least 6 months post treatment and in complete remission, have no history of neurologic disorders and be fluent in Dutch. Members noted 19 patients were included and results from these patients were compared to a control group of 19 patients selected from a database of patients with hematologic malignancy who had undergone systemic chemo, radiotherapy or both. Members noted that 63% of PCNSL patients had mild to moderate impairment on a neuropsychological test and 21% had severe impairment, compared with only 11% of the control group presenting with mild to moderate impairment. Further, of the PCNSL patients 42% were able to attend work with the majority working at a lower level that previously compared with 81% of the control group. Members noted that the authors concluded that the balance between prolongation of PCNSL disease-free survival and the risk of neurotoxicity with MBVP treatment needs to be monitored carefully.
- 7.10. The Committee noted that the optimal chemotherapy treatment regimen for patients with PCNSL remains poorly defined due to a lack of comparative trials. Members noted that NCCN guidelines for PCNSL recommend high dose methotrexate followed by radiation therapy combined with vincristine, procarbazine and cytarabine with or without rituximab.
- 7.11. The Committee considered MBVP did not constitute a standard regimen for PCNSL and that there were other funded treatment regimens that likely had similar effect and were better tolerated, for example high dose methotrexate and cytarabine. The Committee considered that whilst MBVP is not the best backbone regimen to use it supported the HOVON 105 PCNSL/ALLG NHL 24 study as it would answer important questions about the benefit and risks of rituximab treatment for PCNSL.

## 8. Temozolomide access widening

### Application

- 8.1. The Committee reviewed an application from a clinician requesting funding for temozolomide beyond the currently funded 6 cycles post radiation therapy for patients with high grade gliomas (anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM)). The Committee also noted letters from a number of other clinicians in support of the application. Members noted that the applicant had requested that patients with grade 4 tumours be able to receive temozolomide for as long as necessary but considered it is reasonable to place a limit of 24 months treatment for patients with grade 3 tumours.

### Recommendation

- 8.2. The Committee **recommended** that, despite the limited evidence, access to temozolomide should be widened as requested, because there was a high health need in this population and the financial impact would be very small because of the limited number of patients and decreasing cost of temozolomide.
- 8.3. The Committee **recommended** the Special Authority criteria for temozolomide be amended as follows with low priority (changes in bold and strikethrough):

Temozolomide – Special Authority – Retail pharmacy

Special Authority for subsidy

Initial application only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1. Either:
  - 1.1. Patient has newly diagnosed glioblastoma multiforme; or
  - 1.2. Patient has newly diagnosed anaplastic astrocytoma\*; and
2. Temozolomide is to be (or has been) given concomitantly with radiotherapy; and
3. Following concomitant treatment adjuvant temozolomide is to be used in 5 day treatment cycles for a maximum of six cycles of 5 days treatment at a maximum dose of 200 mg/m<sup>2</sup> per day.

**Renewal application only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:**

**All of the following:**

1. **Either:**
  - 1.1. **Both:**
    - 1.1.1. **Patient has glioblastoma multiforme; and**
    - 1.1.2. **The treatment remains appropriate and the patient is benefitting from treatment; or**
  - 1.2. **All of the following**
    - 1.2.1. **Patient has anaplastic astrocytoma\*; and**
    - 1.2.2. **The treatment remains appropriate and the patient is benefitting from treatment ; and**
    - 1.2.3. **Adjuvant temozolomide is to be used for a maximum of 24 months.**

Notes: Indication marked with a \* is an Unapproved Indication. Temozolomide is not subsidised for the treatment of relapsed glioblastoma multiforme. ~~Reapplications will not be approved.~~ Studies of temozolomide show that its benefit is predominantly in those patients with a good performance status (WHO grade 0 or 1 or Karnofsky score >80), and in patients who have had at least a partial resection of the tumour.

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

- 8.5. The Committee noted that the application had been reviewed by the Cancer Treatments Subcommittee (CaTSoP) at its March 2014 meeting.
- 8.6. The Committee noted that it and CaTSoP had considered a number of previous applications for widening of access to temozolomide, including a request in 2007 to extend funded treatment duration and that at that time it recommended the application be declined. However, members noted that since that time the price of temozolomide had decreased by approximately 80% and further price decreases are expected in the future.
- 8.7. The Committee noted that high grade gliomas were not curable with treatment aimed at reducing symptoms and prolonging disease free progression and survival times.
- 8.8. The Committee noted that the current funding of temozolomide is based on the Stupp study (Stupp et al N Engl J Med 2005;352:987-96; Stupp et al Lancet Oncol. 2009;10(5):459) and considered that this remains the primary evidence for temozolomide in patients with GBM. Members noted that in this study median overall survival for

patients treated with temozolomide was 14.6 months with median progression free survival of 6.9 months. Members noted that 78% of patients started adjuvant temozolomide, median number of adjuvant cycles completed was 3 with 47% of patients completing the protocol defined 6 cycles. Members noted that the majority of withdrawals were due to early disease progression or tolerability, but there is a tail of people who tolerated treatment well.

- 8.9. The Committee noted that in the Stupp study at disease progression 60% of control arm patients crossed over to temozolomide, and 25% of interventional arm patients were rechallenged with temozolomide. Members considered that analysis of this data supported the concept of treatment beyond 6 cycles in patients responding to treatment and that this non-randomised evidence had not previously been considered.
- 8.10. The Committee noted that the applicant had provided a series of retrospective studies that examined the outcome for patients receiving adjuvant temozolomide for various durations. Members considered that overall the evidence provided indicated that increasing duration of temozolomide may increase overall survival and progression free survival by 0-2 months at best. However, members considered that the evidence supporting increased duration of temozolomide was of weak strength and quality and likely subject to significant bias.
- 8.11. The Committee noted that several international guidelines recommended use of temozolomide beyond 6 cycles in patients responding to treatment, and therefore considered it highly unlikely that there would ever be quality evidence from a randomised controlled study comparing different treatment durations.
- 8.12. The Committee did not consider it appropriate to remove the Special Authority criteria from temozolomide at this time. Members considered that although its cost had reduced significantly it remained expensive compared with some alternative treatments in some disease settings. Members considered that in particular there would be significant financial risk from increased use in melanoma if the Special Authority criteria were removed completely.

## 9. Nicotine inhaler and oral spray for smoking cessation

### Application

- 9.1. The Committee reviewed submissions from clinicians in support of applications to fund nicotine inhaler (Nicorette Inhalator) and nicotine oral spray (Nicorette QuickMist Mouth Spray) on the Pharmaceutical Schedule for use in the community for smoking cessation.

### Recommendation

- 9.2. The Committee **recommended** that nicotine inhalers and/or nicotine oral spray be listed on the Pharmaceutical Schedule only if the average daily cost of each treatment was no more expensive than the weighted combined average daily cost of the currently funded nicotine presentations (gum, lozenges and patches).
- 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; (iv) The clinical benefits and risks of pharmaceuticals; (v) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule; (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

## Discussion

- 9.4. The Committee noted its previous discussions and recommendations in relation to nicotine inhalers and oral spray. The Committee noted that in May 2013 it had recommended that the applications to fund nicotine inhaler and oral spray in the community be declined primarily on the basis that there was no strong evidence that these preparations are more effective than the currently funded forms of NRT and that funding additional NRT preparations would be associated with considerable expenditure without significant additional health gain. The Committee noted that in February 2014 it had again recommended that the application for funding of nicotine inhaler in the community be declined.
- 9.5. The Committee noted submissions from a clinician in support of funding nicotine inhaler and oral spray, which included a 2013 Cochrane network meta-analysis (Cahill et al. Cochrane Database Syst Rev 2013;5:CD009329) and preliminary unpublished results of a community-based study and a survey of smoking cessation workers.
- 9.6. The Committee considered that the key findings of relevance from the Cahill et al (2013) publication were that “Other” (inhalers, sprays, tablets and lozenges) nicotine presentations marginally increased the odds of quitting versus nicotine gum (OR 1.21; 95% CI 1.01 to 1.46), were comparable to but not superior to nicotine patches (OR 1.07, 95% CI 0.91 to 1.26), and were marginally less effective than combination NRT (OR 1.34, 95% CI 1.00 to 1.80 in favour of the combined therapy). The Committee noted that no trials in the network meta-analysis compared gum with any formulation of ‘other’ NRT.
- 9.7. The Committee noted that the preliminary unpublished data of a study offering smokers the chance to sample a range of NRT from community-based locations such as kiosks in shopping malls provided in the clinician’s submission suggested that nicotine inhaler and oral spray were more popular than funded NRT options. Members noted that there may be factors such as how the inhaler and spray are advertised or promoted (e.g. as ‘new’) which, if in place at the time of the survey, may have influenced smoker choice.
- 9.8. The Committee noted that the clinician’s submission also included results of a brief online survey of 61 smoking cessation community workers which indicated strong sector support for funding nicotine inhaler and oral spray.
- 9.9. The Committee noted a recent publication of a New Zealand-based double-blind randomised controlled trial in 1,423 smokers that compared nicotine mouth spray (1 mg per spray) plus nicotine patch with a placebo mouth spray plus nicotine patch (Caldwell et al. Nicotine Tob Res 2014, May 28. pii: ntu084. [Epub ahead of print]). The primary outcome measure was prolonged abstinence at 12 months. The Committee considered that this was a well-conducted trial although members noted that a large proportion of patients were lost to follow-up and less than 15% of patients completed the 12 month visit. The Committee noted that the intervention group (i.e. the group that received nicotine mouth spray in addition to nicotine patch) yielded significantly higher prolonged and 7-day point prevalence abstinence rates at 1, 3 and 6 months. The primary outcome (prolonged 12-month abstinence) was 10.1% in the intervention group compared with 7.1% in the placebo group (placebo mouth spray plus nicotine patch) (OR 1.47, 95% CI 1.01-2.12), which was statistically significant ( $p=0.045$ ). Secondary outcomes (not smoked in 2 consecutive weeks and biochemically verified abstinence in the last 7 days) did not show statistically significant differences beyond 6 months. Māori study participants had significantly lower abstinence rates, used the spray less often and reported more severe side-effects than non-Māori.
- 9.10. The Committee noted a submission from the Auckland Regional Public Health Service in support of funding nicotine inhalers and oral spray that was received by PHARMAC staff as part of feedback on a commercial proposal PHARMAC had consulted on earlier in the year. The submission highlighted a publication of a single-blind randomised controlled trial conducted in New Zealand in 1,410 adult smokers calling Quitline who were randomised

to usual Quitline care or were sent a box containing NRT products (patch, gum, inhaler, sublingual tablet or oral pouch) to try for a week then choose one or two products to use for eight weeks (Walker et al. *Addiction* 2011;106(6):1176-1185). The primary outcome was 7-day point prevalence abstinence after 6 months. The Committee noted that smokers given a choice of products were more likely to choose the patch and inhaler (34%) and were more likely to have 7-day point prevalence abstinence at 3 months (relative risk 1.17, CI 1.02-1.35), had a longer time to relapse (median 70 days vs 28 days  $p < 0.01$ ) and used more NRT. However, no differences in 6 month 7-day point prevalence or continuous abstinence were found between the groups. The Committee noted that the study authors comment that the study was underpowered to detect differences in quit rates according to specific NRT combinations and that the authors stated that their findings may support the statement: “choice of NRT does not necessarily improve cessation outcome, suggesting that there is nothing to be lost by restricting patients choice of products due to issues such as cost or practicability”.

- 9.11. Overall, the Committee considered that the available evidence did not support improvements in long-term (>6 months) abstinence rates with the use of nicotine inhaler and oral spray compared with the currently funded NRT formulations.
- 9.12. The Committee considered that no evidence had been provided to suggest that availability of nicotine inhaler or oral spray would increase the number of quit attempts or the proportion of successful quit attempts.
- 9.13. However, the Committee considered that the evidence provided suggested that, if funded, it was highly likely that a large proportion (potentially up to 90%, especially if promoted by smoking cessation workers as novel or more effective) of patients could choose to use nicotine inhaler or oral spray as their preferred NRT formulation at their next quit attempt. The Committee considered that given that best practice is combination therapy it was likely that most (at least 75%) patients would be encouraged to use the new formulation(s) in combination with other NRT formulations such as patches or gum. The Committee considered that a proportion of smokers would use spray or inhalers instead of any currently funded formulation because they may be more practical or better tolerated (for example where patients have dentures so can't use gum, or where patients get skin reactions from patches).
- 9.14. Given the lack of robust evidence of benefit beyond 6 months, and the potential for a large proportion of smokers to use the new formulations if funded, the Committee considered that there would be no clinical or financial justification to fund the new presentations if they were more expensive than the average weighted daily cost of the existing funded treatments.
- 9.15. The Committee noted that there was already a large range of funded pharmacotherapy options, including nicotine, bupropion, nortriptyline and varenicline.

## 10. Nicotine replacement therapy (NRT) sample packs

### Application

- 10.1. The Committee reviewed an application from Waitemata DHB Smokefree Services on behalf of other smoking cessation service providers for the funding of nicotine replacement therapy (NRT; nicotine gum, lozenges and patches) in small 'sample' packs for sampling and demonstration purposes.

### Recommendation

- 10.2. The Committee **recommended** that nicotine gum, lozenges and patches should only be funded in 'sample' pack sizes only if the unit cost (i.e. the cost of a single piece of gum or

lozenge or a single patch) was no more expensive than the unit cost of these presentations in the existing funded pack sizes.

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

- 10.4. The Committee noted that PHARMAC currently funds the Habitrol brand of nicotine gum, lozenges and patches (nicotine replacement therapy; NRT), via four mechanisms: dispensed from pharmacy on prescription, dispensed from pharmacy on a Quit Card, supplied directly to patients by "Authorised Providers," and supplied directly to patients in DHB hospitals.
- 10.5. The Committee noted that Authorised Providers include Prison Services, Māori Health Services and Primary Health Units. Authorised Providers order NRT from PHARMAOnline and it is delivered to them in bulk four times a year.
- 10.6. The Committee noted that the currently funded pack sizes of NRT (28 patches, 216 lozenges and 384 pieces of gum) equate to approximately four weeks' treatment. The Committee noted that community smoking cessation providers wish to provide patients with smaller quantities than a whole pack, for sampling and demonstration purposes, but are currently prevented from providing patients with smaller quantities due to legislative requirements around breaking down original packs, re-packaging, and supply of pharmaceuticals outside of their original packaging – all of which are permitted only by doctors, pharmacists and other parties specifically licenced to do so.
- 10.7. The Committee considered that if PHARMAC were to fund sample packs, this would only be necessary for Authorised Providers, given that doctors and pharmacists can legally split the large packs.
- 10.8. The Committee noted that current annual community expenditure on NRT was relatively high at \$6.7 million and that the recent price reductions for NRT (expected to reduce annual expenditure to approximately \$4.4 million) were only made possible by the economies of scale that large pack sizes afford.
- 10.9. The Committee noted that two key benefits of sample packs outlined in the Application were to encourage more smokers to commit to a quit attempt and to reduce waste.
- 10.10. The Committee noted and discussed the results of several publications provided by the applicant in support of funding sample packs, including Beard et al (Tobacco Control 2013;22:118-22 (epub Dec 2011)), Cummings et al (J Pub Health Management & Practice 2006;12:37-43), Bush et al. (Nicotine & Tobacco Res 2008;10:1511-16), Carpenter et al (Arch Intern Med 2011;171:1901-07), Jardin et al (Nicotine & Tobacco Res 2014;16:992-999). The Committee considered that the level of evidence provided was weak to moderate.
- 10.11. The Committee considered that the findings reported in the Jardin et al (2014), Carpenter et al (2011) and Cummings et al (2006) publications supported the notion that NRT sampling could increase the number of people making a quit attempt by between 3% and 22%, particularly in unmotivated smokers.
- 10.12. However, the Committee noted that in the Cummings study patients who were given 6-week sample packs had higher 7-day point prevalence quit rates than patients who were given 1-week sample packs; in the Carpenter study there was no significant difference between sample and non-sample groups in "floating" abstinence and 7-day point prevalence abstinence after 6 months; and in the Jardin study there was no significant

difference between sample and non-sample groups in 7-day point prevalence abstinence across the follow-up period.

- 10.13. The Committee considered that if sample packs were available funded for Authorised Providers, sample packs could replace up to 20% of the larger pack sizes, although the Committee considered it likely that patients would be given more than one sample pack (e.g. multiple sample packs of different flavours or formulations) and members were unsure to what extent 'unsanctioned' sampling was already occurring.
- 10.14. The Committee noted that although there is evidence to support the use of sampling to increase quit attempts, and it is well known that the use of NRT during a quit attempt improves abstinence rates versus no NRT, there was no robust evidence provided that NRT sampling leads to longer-term improvements in abstinence rates versus no sampling.
- 10.15. The Committee considered that based on indicative pricing from the supplier for the sample packs, the availability of funded sample packs would be unlikely to generate financial savings to the Combined Pharmaceutical Budget from reduced wastage of NRT in the larger packs.
- 10.16. Therefore, while Members supported the idea of the use of sample packs, the Committee considered that there was no clinical or financial justification for the unit price of NRT to be more expensive in a smaller pack than a larger one.
- 10.17. The Committee considered that if it was not possible to achieve this – which from the indicative pricing of the sample packs appears would be the case – community based providers have the option of seeking permission from the Ministry of Health to split packs or repackage NRT, for example under regulation 45 of the Medicines Regulations 1984. Members considered that this approach could be more productive in the long run as it is likely that PHARMAC would continue to fund NRT in the larger pack sizes that provide the best value for money.

## 11. Selective cyclooxygenase-2 (COX-2) inhibitors

### Application

- 11.1. The Committee reviewed information from PHARMAC staff in relation to cyclooxygenase-2 (COX-2) inhibitors.

### Recommendation

- 11.2. The Committee **recommended** that a selective cyclooxygenase-2 (COX-2) inhibitor be listed in Section B of the Pharmaceutical Schedule and on the Hospital Medicines List (HML) without restrictions only if it was no more expensive than the weighted combined average daily cost of the currently funded non-steroidal anti-inflammatory drugs (NSAIDs) with a low priority.
- 11.3. 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 11.4. The Committee noted that it had previously reviewed funding applications for the selective COX-2 inhibitors meloxicam, celecoxib, rofecoxib and etoricoxib over a period from 1999 to 2003.

- 11.5. The Committee noted that in 2003 the PHARMAC Board had declined the community funding applications for COX-2 inhibitors, largely on the basis that the treatments provided similar benefit to the funded non-steroidal anti-inflammatory drugs (NSAIDs) with significantly higher costs.
- 11.6. The Committee noted that in 2010 the PHARMAC Board approved the funding of meloxicam as a second-line treatment for patients with haemophilic arthropathy. The Committee noted that celecoxib, etoricoxib and meloxicam are also listed on the Hospital Medicines List (HML) for perioperative use for a total of up to 8 days' use.
- 11.7. The Committee noted that serious cardiovascular safety concerns emerged publicly for rofecoxib and valdecoxib and both products were withdrawn from the market in September 2004 and April 2005, respectively. At that time cardiovascular risks associated with NSAIDs were not well established.
- 11.8. The Committee noted that celecoxib, etoricoxib and meloxicam were the only oral COX 2 inhibitors currently registered in New Zealand.
- 11.9. The Committee noted PHARMAC staff were seeking updated advice from PTAC on the clinical benefits and risks of selective COX-2 inhibitors versus the currently funded NSAIDs in light of newer clinical information and generic competition.
- 11.10. The Committee noted that functions of COX 1 and COX 2 enzymes are well known and NSAIDs inhibit both COX 1 and COX 2. Increasing degrees of selectivity for COX-2 are associated with augmented cardiovascular risk, whereas increasing degrees of selectivity for COX-1 are associated with augmented gastrointestinal (GI) risk. Both selective COX-2 inhibitors and traditional NSAIDs have varying degrees of COX-2 selectivity. Members considered that this has important implications for interpretation of clinical trials. For example, a trial such as VIGOR (Vioxx Gastrointestinal Outcomes Research Trial) is more likely to yield a signal of harm from a COX-2-selective agent given the comparison with naproxen. In contrast, a comparison of etoricoxib with diclofenac, as in EDGE (Etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness Trial) is likely to yield similar risk profiles of the two agents but is unable to provide insight into other clinically important issues such as the relative risk of either etoricoxib or diclofenac against placebo or less COX-2-selective NSAIDs. Therefore, the Committee noted that meta-analyses comparing COX 2 agents as a group with traditional NSAIDs need to be interpreted with some caution.
- 11.11. The Committee noted that meloxicam is an NSAID of the "oxicam" class that acts by inhibiting prostaglandin synthesis with selective COX-2 inhibition. Members noted that some authorities do not consider meloxicam to be a "true" COX-2 inhibitor, but rather an NSAID with COX-2 selective effects. In contrast, the "coxibs" are considered to be true COX 2 inhibitors.
- 11.12. The Committee noted that long-term placebo- and active-controlled trials are not available for the non-selective NSAIDs, with the exception of some large COX-2 studies where certain non-selective NSAIDs were used as active controls in studies of selective COX-2 inhibitors.
- 11.13. Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and non-selective NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs. The Committee noted that the SCOTLSSS trial (The Standard Care Versus Celecoxib Outcome Trial), a large Phase 4 streamline safety study designed to compare the cardiovascular safety of celecoxib versus traditional non-selective NSAIDs may better address this question, with results expected to be reported in 2015.
- 11.14. The Committee considered that the strength and quality of evidence to support selective COX-2 inhibitors providing similar efficacy to funded NSAIDs is high. The Committee

considered that for celecoxib compared with NSAIDs there is good quality evidence in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute analgesia, and for etoricoxib compared with NSAIDs there is good randomised controlled trial evidence for treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, chronic back pain, acute gouty arthritis and acute pain. Members considered that similar evidence is available for meloxicam.

- 11.15. The Committee reviewed a number of studies/publications in which differences in adverse effects between COX-2 inhibitors and non-selective NSAIDs were examined, including but not limited to:
- Bhala et al. Coxib and traditional NSAID Trialists' Collaboration. *Lancet* 2013;382:769-79;
  - MacDonald et al. *Int J Clin Pract.* 2010;64:746-55;
  - Kimmel et al. *Ann Intern Med.* 2005;142:157-64;
  - Chen et al. *Health Technol Assess.* 2008;12:1-278;
  - Antman et al. *Circulation* 2007;115:1634-42;
  - McGettigan & Henry *PLoS Med.* 2011;8:e1001098;
  - Varas-Lorenzo et al. *Pharmacoepidemiol Drug Saf.* 2011;20:1225-36;
  - Jarupongprapa et al. *J Gastroenterol* 2013;48:830-838;
  - Masclee et al. *Aliment Pharmacol Ther.* 2013;38:178-89;
  - Rostom et al. *Clin Gastroenterol Hepatol* 2007;5:818-28;
  - MacDonald et al. *Gut* 2003;52:1265-70;
  - Goldstein et al. *Aliment Pharmacol Ther* 2007;25:1211-22;
  - Chang et al. *Gut* 2011;60:1372-8.
- 11.16. In summary, the Committee considered that all selective COX-2 inhibitors are associated with increased cardiovascular risks. The Committee considered that the best evidence is available for celecoxib and the relative risk (RR) appears to be 1.37 compared to placebo; data on meloxicam is inconclusive but the relative risk appears to be above 1.0; and etoricoxib may have higher myocardial infarction (MI) rate compared with celecoxib. With regards to stroke risk the Committee considered there is limited data.
- 11.17. The Committee noted that all selective COX-2 inhibitors and nonselective NSAIDs are associated with hypertension and fluid retention. Evidence suggests that naproxen appears to be cardioprotective in terms of reducing MI and that low-dose ibuprofen may not result in increased MI due to prolonged inhibition of COX-1. The Committee considered that the available evidence suggests that diclofenac and high-dose ibuprofen are associated with increased risk of MI similar to that of the coxibs.
- 11.18. The Committee considered that the available evidence suggests that all selective COX-2 inhibitors appear to be associated with less GI side effects than nonselective NSAIDs but it is difficult to quantify the benefit long term. The gradient seems to be related to degree of COX-2 selectivity in following order (most selective first): celecoxib, ibuprofen, diclofenac, meloxicam (high dose), tenoxicam and naproxen. Members noted that there was evidence to suggest that concurrent use of aspirin with a selective COX-2 inhibitor is likely to nullify the benefit.
- 11.19. The Committee considered that it was difficult to quantify the extent to which differences in side effect profiles of the selective COX-2 inhibitors and nonselective NSAIDs would affect compliance with treatment or clinical outcomes. The Committee noted that there was some evidence to suggest that adherence to a gastroprotective agent (GPA, such as a proton pump inhibitor, PPI) in patients taking NSAIDs is relatively low (68% in one European study; van Soest et al. *Gut* 2011;60:1650-9). Suboptimal adherence to GPAs has been associated with a 2.5- to 4-fold increase in the risk of upper GI bleeding in traditional NSAID users. The Committee noted that if adherence to selective COX-2 inhibitors is higher than GPAs+non-selective NSAIDs it could reduce the risk of upper GI bleeds.

- 11.20. The Committee considered that there may be a place for selective COX-2 inhibitors plus PPI in patients with high GI risk in improving GI bleeds. For example, a publication by Chan et al (Lancet 2007;369:1621-6) reported that high-risk patients (prior upper GI bleeding) who were treated with combined therapy (esomeprazole plus celecoxib) for one year had no recurrent ulcer bleeding compared with a recurrence rate of 9% in those treated with celecoxib alone. However, results of another study suggest that, in very high-risk patients, neither a selective COX-2 inhibitor administered on its own nor the combination of a nonselective NSAID and a PPI will reduce the risk of ulcer recurrence or rebleeding (Chan et al. Gastroenterology 2004;127:1038–43).
- 11.21. In considering which (if any) of the funded NSAIDs is similar to the selective COX-2 inhibitors, the Committee considered that diclofenac and sulindac may have similar COX-2 selectivity to meloxicam and celecoxib. However, clinical trials have reported higher incidence of upper GI complications with diclofenac compared with celecoxib, and diclofenac is also associated with higher incidence of stroke. The Committee was not aware of comparative data for sulindac. Members noted that some studies have shown similar GI complications between etoricoxib and meloxicam (higher than celecoxib).
- 11.22. The Committee considered that in low-risk patients the use of selective COX-2 inhibitors instead of nonselective NSAID plus PPI could result in benefits in terms of PPI avoidance, noting that PPI use has been associated with high risk of pneumonia, low magnesium levels causing symptoms, low calcium absorption, hyponatraemia, interstitial nephritis and osteoporosis.
- 11.23. The Committee considered that the funded alternative treatment options for patients who cannot tolerate the GI side effects of funded NSAIDs would be paracetamol, tramadol, codeine and other opioids. The Committee considered that there were no problems with access to those treatments but they too have side effects.
- 11.24. The Committee considered that the efficacy of the three registered COX-2 inhibitors was probably similar but some studies quoted in Chen et al (Health Technol Assess. 2008;12(11):1-278) suggested equivalence or slight inferiority of meloxicam compared with NSAIDs. The Committee considered that the side effect profiles of the three registered COX-2 inhibitors are probably similar but direct comparisons are lacking. The Committee noted that celecoxib could be administered once or twice daily whereas meloxicam and etoricoxib are administered daily.
- 11.25. The Committee considered that, in general, selective COX-2 inhibitors would provide no efficacy benefit over currently funded NSAIDs, although they may provide marginal benefits in terms of reduced GI effects in patients taking these agents chronically, particularly in patients with moderate to high risk of GI problems.
- 11.26. The Committee reviewed the assumptions used in a previous cost-effectiveness analysis conducted for PHARMAC (Technology Assessment Report [TAR] 55). The Committee considered the utility values were reasonable, except members considered that complicated GI ulcers requiring surgery is likely to have much lower utility. The Committee considered that these patients are likely to have greater morbidity than patients surviving MI, noting that patients with MI are unlikely to be hospitalised for 6 days with modern management. The Committee considered that with respect to GI events it is reasonable to assume the benefits and risks used in TAR 55. The Committee considered that it is reasonable to assume that the withdrawal rates between selective COX-2 inhibitors and traditional NSAIDs would be similar but withdrawal rates with COX-2 inhibitors could be lower because of lower incidence of GI effects. The Committee considered that the analysis should assume that the risk of MI with selective COX-2 inhibitors and nonselective NSAIDs is similar. Members noted that the costs of the selective COX-2 inhibitors and comparator treatments would need to be adjusted to reflect current pricing.
- 11.27. The Committee noted that a large proportion of patients (at least 50%) would likely take selective COX-2 inhibitors for a very short duration (one month or less), as evidenced in

overseas markets. The Committee considered that this pattern of use is unlikely to be different from the use of funded nonselective NSAIDs.

- 11.28. The Committee noted that there is some evidence to suggest that there may be a potential benefit from selective COX-2 inhibitors in prevention of colorectal cancer (Bertagnolli M. *Lancet Oncol* 2007;8:439-43), which could be considered in the cost-utility analysis. In addition, there may be reduced incidence of lower GI events with selective COX-2 inhibitors.
- 11.29. The Committee considered that the doses of the selective COX-2 inhibitors and comparator treatments used by PHARMAC staff for financial analyses were reasonable, both for short- and long-term treatment.
- 11.30. The Committee considered that, if funded, the main use of selective COX-2 inhibitors would be for chronic inflammatory pain, acute postoperative pain and acute soft tissue injury.
- 11.31. The Committee considered that the patient populations that would most benefit from selective COX-2 inhibitors would be patients with a low cardiovascular risk who have had GI side effects from nonselective NSAIDs, patients with high risk colonic polyps who need to be on NSAIDs, and patients who had adverse effects from PPIs.
- 11.32. The Committee considered that if selective COX-2 inhibitors were funded they would mainly replace the use of funded NSAIDs, paracetamol and tramadol, although members were uncertain as to the extent of this replacement, noting that, with the exception of patients with high cardiovascular risk who require chronic treatment, in general any patient taking a funded NSAID could take a selective COX-2 inhibitor.
- 11.33. The Committee considered that there was no particular funded NSAID/formulation that would be more likely to be replaced by a selective COX-2 inhibitor than any other funded NSAID/formulation, although members speculated that patients on long-acting NSAID formulations might be more likely to switch to a selective COX-2 inhibitor if funded.
- 11.34. The Committee considered that the funded “pain relief” market would grow substantially overall if selective COX-2 inhibitors were funded because they would likely replace some of the use of over the counter paracetamol and NSAIDs as well as encompassing the current private market for selective COX-2 inhibitors.
- 11.35. The Committee considered it unlikely that funding selective COX-2 inhibitors would significantly reduce the use of funded GPAs, noting that these would still be needed in some patients taking selective COX-2 inhibitors.
- 11.36. The Committee considered that there was no clinical reason not to fund a selective COX-2 inhibitor, and that it would be useful to have a wider range of treatment options. However, members considered that the unmet clinical need was low and there was no particular justification for selective COX-2 inhibitors to be funded at a higher price than the average cost of current treatments. Similarly, the Committee considered that there would be no particular reason to restrict access to COX-2 inhibitors if they were funded at a similar price point to the currently funded NSAIDs.
- 11.37. The Committee considered that it would be reasonable for PHARMAC to run a competitive process for just one selective COX-2 inhibitor to be funded. However, the Committee considered that if that was the strategy PHARMAC decided to employ, it may be preferable to limit it to the “coxib” class (i.e. excluding meloxicam), noting that meloxicam is not considered a ‘true’ COX-2 inhibitor as it inhibits COX-1 at a 15 mg dose. The Committee considered that if pricing of the “coxibs” was similar, celecoxib would be the preferred agent as it has the best evidence base for risks and benefits.

11.38. The Committee considered that if PHARMAC was to fund a COX-2 inhibitor this should be accompanied by prescriber education.

## 12. Melatonin for insomnia secondary to neurodevelopmental disorders in children and adolescents

### Application

12.1. The Committee reviewed submissions relating to an application to fund melatonin for the treatment of insomnia secondary to neurodevelopmental disorders in children and adolescents.

### Recommendation

12.2. The Committee **recommended** that melatonin 2 mg modified-release tablets (Circadin) be listed in the Pharmaceutical Schedule for insomnia secondary to neurodevelopmental disorders in children and adolescents, subject to the following Special Authority restrictions, with a low priority:

**Initial application** only from a psychiatrist, paediatrician, neurologist or respiratory specialist, or medical practitioner on the recommendation of a psychiatrist, paediatrician, neurologist or respiratory specialist. Approvals valid for 12 months for applications meeting the following criteria:

- 1 Patient has been diagnosed with persistent and distressing insomnia secondary to a neurodevelopmental disorder (including, but not limited to, autism spectrum disorder or attention deficit hyperactivity disorder); and
- 2 Behavioural and environmental approaches have been tried or are inappropriate; and
- 3 Melatonin is to be given at doses no greater than 6 mg per day; and
- 4 Patient is aged  $\leq 18$  years.

**Renewal application** only from a psychiatrist, paediatrician, neurologist or respiratory specialist, or medical practitioner on the recommendation of a psychiatrist, paediatrician, neurologist or respiratory specialist. Approvals valid for 12 months for applications meeting the following criteria:

- 1 Patient is aged  $\leq 18$  years; and
- 2 Patient has demonstrated clinically meaningful benefit from melatonin (clinician determined); and
- 3 Patient has had a trial of melatonin discontinuation within the past 12 months and has had a recurrence of persistent and distressing insomnia; and
- 4 Melatonin is to be given at doses no greater than 6 mg per day.

12.3. The Committee **recommended** that the restrictions applying to melatonin on the Hospital Medicines List (HML) be amended to include the same criteria as recommended for the community Special Authority, above, with a low priority. Further, the Committee **recommended** that the unregistered immediate-release presentations of melatonin (tab 1, 2, and 3 mg and cap 2 mg and 3 mg) be delisted from the HML.

12.4. 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;* (vii) *The direct cost to health service users.*

### Discussion

12.5. The Committee noted that in November 2012, PTAC reviewed an application from Aspen to fund melatonin 2 mg modified-release (MR) tablets (Circadin) for primary insomnia in patients aged at least 55 years, as well as clinician-initiated applications for melatonin in two off-label indications: insomnia secondary to dementia and insomnia secondary to neurodevelopmental or psychiatric disorders in children and adolescents.

- 12.6. The Committee noted that at the time it had recommended that the applications for primary insomnia in patients aged at least 55 years and for insomnia secondary to dementia be declined, and had also recommended that melatonin be funded for insomnia secondary to neurodevelopmental disorders such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) in patients  $\leq$  18 years of age with a low priority.
- 12.7. The Committee noted that the original application for melatonin for insomnia secondary to a neurodevelopmental disorder was made by a clinician group and had not specified a particular formulation of melatonin, nor did PTAC's recommendation specify a particular formulation.
- 12.8. The Committee noted that in May 2014 PHARMAC staff consulted on a proposal to fund melatonin 2 mg MR tablets (Circadin) — the only registered melatonin presentation in New Zealand — subject to Special Authority criteria as recommended by PTAC. The consultation letter also included a proposal to delist the immediate-release (IR) presentations from the Hospital Medicines List (HML), given the availability of a registered presentation.
- 12.9. The Committee noted that while consultation responses were generally supportive of the concept of funding melatonin for the proposed patient group, a number of issues were raised with various aspects of the proposal, which PHARMAC staff considered required further clinical advice from PTAC.
- 12.10. The Committee noted that melatonin is classified as a prescription medicine in New Zealand meaning that all unregistered brands must be prescribed and supplied in accordance with the requirements of sections 25, 26 and 29, as applicable, of the Medicines Act 1981. The Committee noted that PHARMAC was not considering funding any unregistered presentations of melatonin, given the availability of a registered presentation; members considered that this was appropriate.
- 12.11. The Committee reviewed a large number of publications provided by consultation responders and by Aspen, as well as a number of overseas public healthcare guidelines on the use of melatonin in children.
- 12.12. The Committee considered that, although the available evidence was weak and there was a lack of direct comparisons between MR and IR formulations, MR melatonin would have a similar efficacy to IR melatonin, providing a reduction in sleep latency of around 30 minutes (Cortesi et al. *J Sleep Res* 2012;21:700-9; De Leersnyder et al. *Pediatr Neurol* 2011;45:23-6). The Committee considered that the optimal time to take the MR preparation to obtain this benefit would be approximately 1 to 2 hours before bedtime.
- 12.13. The Committee considered that, based on findings from the clinical trials, a dose of 4 mg to 6 mg of MR melatonin would typically be used for optimal effect in children. The Committee considered that an average of 5 mg daily would be reasonable for the purposes of PHARMAC's analyses.
- 12.14. The Committee considered that there was no evidence to suggest that doses of MR melatonin higher than 6 mg daily would provide greater efficacy than doses of 4–6 mg per day and, therefore, if melatonin was funded it would be reasonable to restrict the funded dose to a maximum of 6 mg daily in order to reduce the fiscal risk.
- 12.15. The Committee considered that for clinical situations where patients cannot swallow whole tablets it would be reasonable to crush the MR tablets, noting that this was not recommended on the datasheet. The Committee noted that this would nullify the MR properties. The Committee considered that in this situation it would be preferable to crush the registered MR presentation compared with an unregistered IR presentation, given the lack of quality controls for the unregistered presentations (including a lack of controls around whether or not a particular brand contains the stated quantity of melatonin). The

Committee considered there was no evidence to suggest that dose adjustment would be needed if the MR tablets were crushed. The Committee noted that overseas guidance recommends crushing Circadin tablets to give an immediate-release profile (e.g. <http://www.swlstg-tr.nhs.uk/uploads/documents/healthcare-professionals/twc21i-melatonin-shared-care-guideline-201309.doc>).

- 12.16. The Committee considered that there was no particular clinical situation where it would only be clinically feasible for an IR presentation of melatonin to be used. Given that there are no regulatory, safety, efficacy, or quality controls for IR melatonin, the Committee considered that it would be preferable to fund in the community, and list on the HML, only the registered brand of melatonin.
- 12.17. The Committee considered that it would be reasonable to include neurologists and respiratory medicine specialists in the permitted Special Authority applicant types, should melatonin be funded, although members considered that the majority of patients meeting the proposed criteria should be under the care of a paediatrician or a child and adolescent psychiatrist.
- 12.18. The Committee considered that patients who take melatonin with good effect would likely continue to take it without interruption for the duration of their eligibility for treatment. Further, the Committee considered it likely that many patients would wish to stay on melatonin for only small or perceived benefits, as it is viewed as a low-risk medicine. The Committee considered that it would be good clinical practice for patients to attempt a discontinuation trial at least once a year in order to determine whether melatonin was still providing a clinically meaningful benefit. Additionally, the Committee considered that given the potential for a substantial budget impact from funding melatonin it would be important to require prescribers to confirm that that patient has had a clinically meaningful benefit from treatment. The Committee considered that this should be a requirement in any Special Authority criteria, along with a requirement for a discontinuation trial.
- 12.19. The Committee considered that the estimated health gains from melatonin used in PHARMAC staff analyses were appropriate, although members noted the difficulty in quantifying these gains.
- 12.20. The Committee considered the patient number assumptions used in the analyses were reasonable, although some members considered that the patient numbers could potentially be higher than estimated, given that the numbers were based on patients with ASD, ADHD and intellectual disabilities accessing treatment whereas there are a number of other patient groups who could meet the proposed indication definition (as noted in the following paragraph). The Committee considered that there was no evidence to suggest that the benefits of melatonin continue after treatment is stopped, so it would be reasonable for the analysis to assume no ongoing benefit after treatment cessation.
- 12.21. The Committee noted that during consultation on the proposal to fund melatonin, PHARMAC had received requests to change the Special Authority wording to provide clarification and further definition of “neurodevelopmental disorder.” The Committee considered that this was not necessary, noting that treating clinicians are capable of appropriately identifying whether or not a patient has a neurodevelopmental disorder (including, for example, patients with learning disabilities, intellectual disabilities, developmental delay, and neurodevelopmental disorders caused by traumatic brain injury). Members noted that the proposed criteria already specified two of the disorders that have been most extensively studied.
- 12.22. The Committee considered that there was no compelling evidence to suggest that insomnia secondary to a neurodevelopmental disorder resolved once patients reached the age of 19. However, the Committee considered that it would be reasonable to restrict funded access to melatonin to patients aged 18 years or under, for fiscal reasons and because there are less expensive funded alternatives for older patients (see below).

- 12.23. The Committee noted that the children and adolescents with insomnia secondary to a neurodevelopmental disorder are a particularly high-need patient group and there are few appropriate treatment options for them. The Committee considered that while this patient group may continue to have a clinical need for treatment once they turn 19, there are a number of funded alternatives which could be reasonably tried in older patients. The Committee noted that these funded alternative treatments have a different side effect profile from melatonin, and can have cognitive side effects and potential for dependency. However, given that PHARMAC had not received a funding application for melatonin in insomnia secondary to a neurodevelopmental disorder in patients aged 19 or older, nor has PTAC assessed the evidence (if any) for melatonin in this age group, the Committee considered that there was no basis for recommending melatonin over the funded alternatives in patients aged 19 or older.

### **13. Glucose 4% with sodium chloride 0.18% solution (“Bart’s solution”) for rehydration**

#### **Application**

- 13.1. The Committee considered information in relation to requests to fund glucose 4% with sodium chloride 0.18% solution (“Bart’s solution”) in DHB hospitals.

#### **Recommendation**

- 13.2. The Committee **recommended** that glucose 4% with sodium chloride 0.18% solution (“Bart’s solution”) not be listed in Part II of Section H of the Pharmaceutical Schedule.
- 13.3. The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals.*

#### **Discussion**

- 13.4. The Committee noted that glucose 4% with sodium chloride 0.18% solution (“Bart’s solution”) is used short term, as one of a number of management options, to maintain normal fluid and electrolyte requirements for patients who are unable to take fluid enterally.
- 13.5. The Committee noted that it had previously recommended that Bart’s solution be excluded from the Hospital Medicines List (HML) following consideration of feedback from the Australian and New Zealand College of Anaesthetists (ANZCA) supporting its exclusion on the basis that Bart’s solution is associated with severe side effects, in particular seizures when used as a rehydration solution in children.
- 13.6. The Committee noted that PHARMAC had subsequently received a number of requests to list Bart’s solution on the HML and that PHARMAC had recently sought additional public feedback on this issue in April 2014. The Committee noted that members of the New Zealand National Committee of ANZCA recently changed their previous recommendation to remove Bart’s solution from the HML to one in support of listing Bart’s solution on the HML as they have been made aware that some practitioners in New Zealand consider Bart’s solution to be useful in some situations, but only on the condition that it is used with careful individual patient assessment and monitoring of patients, and only as a maintenance fluid therapy.
- 13.7. The Committee noted that paediatric fluid prescribing for the last six decades has been based on a publication by Holliday and Segar (Paediatrics 1957;19(5):823-32). The calculation for fluid requirements in the publication was based on an estimation of the energy expenditure at rest and that of normal activity. The Committee considered that this formula is crude and does not take into consideration any losses associated with various

common childhood illnesses, like gastroenteritis, or the increased metabolic demands and inappropriate antidiuretic hormone (ADH) secretion that occurs commonly with paediatric illnesses for which fluids are prescribed.

- 13.8. The Committee noted that there have been several reports of deaths or brain damage in children in the past 20 years from the prescription of hypotonic maintenance fluid to children, predominantly glucose 4% with sodium chloride 0.18% solution, many of which were considered preventable. The Committee noted that in 2007 Bart's solution was removed from general paediatric wards in the United Kingdom, apart from use in liver, renal, cardiac and intensive care units. The 2013 chief paediatrician's fluid standards for paediatric patients in New South Wales guideline supports a similar stance of not using Bart's solution with the use of 0.45% and 0.9% sodium chloride containing fluids only being recommended.
- 13.9. The Committee noted a meta-analysis of 10 trials comparing hypotonic with isotonic maintenance fluids in children which showed an increased risk of developing hyponatremia (RR 2.24, 95% CI 1.52 to 3.31) and severe hyponatremia (RR 5.29, 95% CI 1.74 to 16.06) with hypotonic maintenance fluid (Wang et al. Paediatrics 2014;133(1):105-13).
- 13.10. Although members felt that the potential for harm in paediatric patients was from inexperienced prescribers as opposed to a safety issue with Bart's solution itself, the Committee noted that there also did not appear to be any particular clinical benefit from, or need for, Bart's solution in the paediatric population compared with available alternatives.
- 13.11. The Committee noted that the majority of hospitals do not use Bart's solution or see a role for it in any adult patients. The Committee noted that the New Zealand committee of ANZCA did not expand on which situations Bart's solution could be useful, or why Bart's solution may be preferred in these situations as opposed to other available fluid solutions.
- 13.12. The Committee noted that the UK National Institute for Health and Care Excellence (NICE) guidelines mention that there are no published trials in adults considering the optimal intravenous fluid regimen for maintenance and that a randomised controlled trial is needed to compare intravenous fluid maintenance regimens with different sodium concentrations (e.g. comparison between sodium chloride 0.18% in glucose 4% and sodium chloride 0.45% in glucose 4% solutions).
- 13.13. Similar to the paediatric situation, the Committee considered that there was no clear evidence for a clinical benefit of Bart's solution in the adult population versus available alternatives. The Committee noted that more than a year had passed since the inception of the HML and most DHBs, including those with the largest intensive care units, had not communicated any issue with the omission of Bart's solution.
- 13.14. The Committee considered that the range of alternative listed fluid options was sufficient for the existing clinical need and, on balance, considered that the risk of harm from listing Bart's solution was too great to justify a listing in the light of any clear unmet clinical need or robust evidence of benefit over alternative options.
- 13.15. The Committee noted that if Bart's solution is not listed on the HML, any centres that had been using Bart's solution for adult patients pre-HML will need to develop new protocols if this has not already been done.