PTAC meeting held on 5 & 6 November 2015

(minutes for web publishing)

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

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

PTAC may:

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

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Chair

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1. Subcommittee Minutes

Cancer Treatments Subcommittee of PTAC (CaTSoP)

1.1. The Committee noted the record of the Cancer Treatments Subcommittee meeting held on 20 March 2015.

1.2. The Committee accepted the recommendations made with the exception of those made in relation to Item 5 (Subcutaneous trastuzumab) and Item 7 (Zoledronic acid for Breast Cancer).

1.3. In relation to item 5, subcutaneous trastuzumab, the Committee noted that it had previously considered this application at its November 2014 meeting. Members noted that they remained concerned about the potential risks of under-dosing associated with the administration of a fixed dose to patients in higher weight ranges.

1.4. The Committee considered that the evidence for the use of subcutaneous trastuzumab for the treatment of patients with HER2 positive breast cancer did not support any clear additional clinical benefit when compared with the currently funded intravenous formulation of trastuzumab. The Committee recommended that subcutaneous trastuzumab should be funded for HER2 positive breast cancer only if cost neutral to the intravenous formulation of trastuzumab, with cost neutrality taking into account future entry of intravenous trastuzumab biosimilars and associated price decreases.

1.5. In relation to item 7, Zoledronic acid for breast cancer, the Committee noted and accepted the Subcommittee's recommendation that zoledronic acid be funded for adjuvant use in postmenopausal women with early breast cancer, with low priority. The Committee noted the meta-analysis discussed by the subcommittee in item 7.11, comprising individual patient data derived from randomised adjuvant bisphosphonate trials in patients with early breast cancer, had recently been published (Coleman et al. Lancet 2015;386:1353-61). The Committee recommended that this evidence be referred to the Cancer Treatments Subcommittee for further consideration.

Respiratory Subcommittee

1.6. The Committee noted the minutes from the Respiratory meeting of 2 September 2015.

1.7. In relation to item 4.9, omalizumab, the Committee noted and accepted the wording changes to the Special Authority criteria, but did not accept the change to number of admissions to hospital from four to two. The Committee recommended waiting a further 12 months to allow more prescription data to accumulate before reviewing the hospital admission criterion and recommended that the Special Authority criteria be again reviewed at the next meeting of the Respiratory Subcommittee.

1.8. The Committee accepted the remainder of the minutes.

Special Foods Subcommittee

1.9. The Committee noted and accepted the minutes from the Special Foods Subcommittee meeting of 22 July 2015.

2. Dabrafenib and trametinib for BRAF V600 mutation-positive unresectable (Stage III) or metastatic (Stage IV) melanoma

Application

2.1. The Committee considered an application from Novartis Pharmaceuticals for the funding of dabrafenib (Tafinlar) and trametinib (Mekinist) for use in combination for the treatment

Chair

of BRAF V600 mutation-positive unresectable (Stage III) or metastatic (Stage IV) melanoma.

Recommendation

2.2. The Committee **recommended** that the application to fund dabrafenib and trametinib for use in combination for the treatment of BRAF V600 mutation-positive unresectable (Stage III) or metastatic (Stage IV) melanoma be declined.

2.3. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee for consideration.

2.4. The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people in 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

2.5. The Committee noted that New Zealand has a high incidence of melanoma and considered that there was an unmet health need for effective new treatments for patients with advanced melanoma.

2.6. The Committee noted that dabrafenib was an oral selective inhibitor of mutated forms of BRAF and that an application to fund dabrafenib as monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma has previously been considered by PTAC in November 2014 and it recommended that the application be declined. Members noted that PTAC had also previously considered funding applications for other treatments for advanced melanoma; vemurafenib (Zelboraf) BRAF V600 mutation positive unresectable (stage IIIC or stage IV) melanoma in May 2013 and ipilimumab (Yervoy) for previously treated unresectable (stage IIIC or stage IV) melanoma in February 2014, both of which were recommended for decline. Members further noted that an application for pembrolizumab for metastatic melanoma stage III or IV is also being considered at this meeting.

2.7. The Committee noted that trametinib is an oral mitogen-activated protein / extracellular signal-regulated kinase (MEK) inhibitor.

2.8. The Committee noted that combination dabrafenib and trametinib treatment was indicated for the subset of advanced melanoma patients with BRAF V600 positive mutations. Members noted that BRAF mutation testing was routinely available in New Zealand but was not currently funded in all centres.

2.9. The Committee considered the key evidence for combination treatment of dabrafenib and trametinib came from the COMBI-D study; a phase III, randomised, double-blind study comparing combination dabrafenib and trametinib to dabrafenib and placebo in previously untreated patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma (Long et al. N Engl J Med 2014; 371: 1877–88. Long et al. Lancet 2015; 386: 444–51 and Schadendorf et al. European Journal of Cancer 2015; 51: 833– 40). Members noted that 947 patients were screened for eligibility, 245 patients were negative for BRAF V600, 248 failed other inclusion criteria and 38 declined to participate in the trial. Members noted that 423 patients were randomly assigned (1:1) to receive dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) (n= 211) or dabrafenib (150 mg twice daily) and placebo (n=212) with treatment continued until disease progression, death, or withdrawal from the study.

2.10. The Committee noted the results of COMBI-D reported in Long et al. Lancet 2015 that as of the final data cut-off (12 January 2015) 99 patients in the dabrafenib / trametinib group versus 123 patients in the dabrafenib group had died (HR of 0·71 (95% CI 0·55–0·92; p=0·0107), and median overall survival (OS) was 25.1 months (95% CI 19.2 – not reached) in the dabrafenib / trametinib arm versus 18.7 months in the dabrafenib only arm (HR 0.71, 95% CI 0.55 – 0.92; p=0.0107). Members noted that investigator assessed median progression free survival (PFS), the primary endpoint of the study, was 11.0 months (95% CI 8.0-13.9) in the dabrafenib / trametinib arm versus 8.8 months (95% CI 5.9-9.3) in the dabrafenib only arm (HR 0·67, 95% CI 0·53–0·84; p=0·0004). Members noted that multiple statistical testing had been carried out. Members noted that treatment-related adverse events occurred in 87% of patients in the dabrafenib / trametinib group and 90% of patients in the dabrafenib only group; the most common AEs in the dabrafenib / trametinib group were pyrexia (52%), chills (28%) and fatigue (27%). Members noted that 11% of patients in the combination arm permanently discontinued treatment due to adverse events, most often pyrexia and ejection fraction decrease, compared with 7% in the monotherapy arm.

2.11. The Committee reviewed supporting evidence from BRF113220; a phase II, open label but assessor blinded, randomised controlled study that compared combination dabrafenib (150 mg) and trametinib (1 or 2 mg) (n=162) with dabrafenib (150 mg) monotherapy (n=85) in patients with metastatic melanoma and BRAF V600 mutations (Flaherty et al. NEJM 2012;367;1694-703). Members noted that patients who had disease progression while receiving monotherapy were permitted to cross over to receive combination treatment and the primary end points were the incidence of cutaneous squamous-cell carcinoma, progression free survival, and response. Members noted that after a median follow up of 14.1 months median PFS was 9.4 months in the combination group compared with 5.8 months in the monotherapy group (HR 0.39; 95% CI 0.25 to 0.62; p<0.001) and overall response rate (ORR) with combination therapy was 76% compared with 54% with monotherapy (p=0.03).

2.12. The Committee noted that median OS from BRF113220 after a median follow up of 24 months (reported separately in J Clin Oncol 2014;32:5s(suppl; abstr 9010) was 23.8 months in the combination group compared with 20.2 months in the monotherapy group (HR 0.73, p=0.24).

2.13. The Committee also noted evidence from Johnson et al. (J Clin Oncol 2014;32:3697-704) which reported outcomes in patients from the dabrafenib monotherapy arm of BRF113220 who had crossed over to combination dabrafenib and trametinib treatment. Members noted that the median PFS of patients that had previously received dabrafenib monotherapy for 6 months or greater was 3.9 months compared with 1.8 months for patients that received dabrafenib monotherapy for less than 6 months (HR 0.4995% CI 2 to 4, p=0.02). Members noted that the most frequent adverse events with combination treatment were pyrexia (58%), nausea (38%), vomiting (35%), fatigue (35%), constipation (31%), diarrhoea (27%), and chills (23%).

2.14. The Committee also reviewed evidence from COMBI-V, an open-label phase III trial in which 704 previously untreated patients with metastatic melanoma with a BRAF V600 mutation were randomly assigned to receive either combination dabrafenib (150 mg twice daily) and trametinib (2 mg daily) or vemurafenib (960 mg twice daily) (Robert et al. NEJM 2015;372:30-9). Members noted that at twelve months OS, the primary endpoint of the study, was 72% in the combination group and 65% in the vemurafenib group (HR 0.69; 95% CI, 0.53 to 0.89; p=0.005) and median PFS was 11.4 months in the combination group compared with 7.3 months in the vemurafenib group (HR, 0.56; 95% CI, 0.46 to 0.69; p<0.001).

2.15. The Committee noted that overall the evidence for the use of combination dabrafenib and trametinib was of good quality and strength and indicated a survival gain for combination treatment over dabrafenib monotherapy. However, members noted that the

studies did not use a comparator for a New Zealand setting as neither dabrafenib or vemurafenib are currently funded in New Zealand.

2.16. The Committee noted a formal indirect treatment comparison of combination dabrafenib / trametinib and dacarbazine treatment had been supplied by the applicant using the results from COMBI-D and BREAK-3: a phase III, open-label, randomized study comparing oral dabrafenib with intravenous dacarbazine in previously untreated patients with BRAF V600E mutation positive advanced (stage III) or metastatic (stage IV) melanoma. Members noted they had previously considered evidence from the BREAK-3 study during consideration of the application for dabrafenib monotherapy in November 2014 (Hauschild et al. Lancet. 2012;380:358-65, Latimer et al. J Clin Onc 2013;31; 9044, and Hauschild et al. unpublished abstract 5785: European Society of Medical Oncology (ESMO) conference 2014). Members noted the results from BREAK-3 indicated that median PFS as assessed by investigator, the primary endpoint of the study, was improved in the dabrafenib group (5.1 months compared with 2.7 months for the dacarbazine group (HR 0.30, 95% CI 0.18 – 0.51; p<0.0001)) and after a median follow-up of 16.9 months, median OS in the dabrafenib arm was 20.0 months compared with 15.6 months in the darcarbazine arm.

2.17. The Committee considered based on this indirect comparison that it was likely that combination dabrafenib and trametinib would provide additional health benefits over dacarbazine treatment for advanced melanoma patients with BRAF V600 mutations in New Zealand but noted that the precise magnitude and duration of benefit was unclear and that combination treatment was associated with increased toxicity. Members considered that patients receiving dabrafenib and trametinib treatment would likely require monitoring of adverse effects and that the effects of non-pharmaceutical costs, in particular the need for monthly liver function tests, baseline and three monthly cardiac assessments, ophthalmology assessments for visual disturbance in around 20% of patients, and at least one fever assessment in 75% of patients (as documented in the MedSafe Datasheet), should be taken into account in any analysis of budget impact and cost-effectiveness.

2.18. The Committee noted the Medsafe datasheet for trametinib identified a significant frequency of adverse events including haemorrhage, cardiomyopathy, disorders associated with visual disturbance, interstitial lung disease, pyrexia, serious skin toxicity and non-cutaneous cell malignancy. Members noted that there appeared to be inconsistency with regards to the reporting of adverse events between the Medsafe approved datasheet and the evidence provided in that the datasheet details 16% of patients with haemorrhagic events in the BRF11320 study however this did not appear to be reported in the relevant study tables in the datasheet. Members considered this may indicate an issue with regards to reliability of reporting from this study.

2.19. The Committee recommended that the application be referred to the Cancer Treatments Subcommittee for consideration. Members considered that the proposed pricing sought for combination treatment was too high given the potential health gains and significant toxicity associated with treatment.

3. Crizotinib for anaplastic lymphoma kinase-positive advanced and metastatic non-small cell lung cancer

Application

3.1. The Committee considered an application from Pfizer NZ Limited for the funding of crizotinib (Xalkori) for the treatment of advanced and metastatic (Stage IIIB and IV) non-small cell lung cancer (NSCLC) patients who test positive for an anaplastic lymphoma kinase (ALK) gene rearrangement in first line (treatment naïve) and second line (following treatment with at least one platinum-based chemotherapy regimen) settings.

Recommendation

3.2. The Committee **recommended** that the application to fund crizotinib as a first line treatment for ALK positive advanced and metastatic NSCLC be declined.

3.3. The Committee **recommended** that the application to fund crizotinib as a second line treatment for ALK positive advanced and metastatic NSCLC be declined.

3.4. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee for consideration.

3.5. The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people in 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

3.6. The Committee noted that lung cancer is the leading cause of cancer death in New Zealand and worldwide. Members noted that lung cancer incidence and mortality are 2–3 times higher in Maori males and 3–4 times higher in Maori females, compared with non-Maori. Members noted that lung cancer can be broadly categorised into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC being the most common type (~80%) in New Zealand. Members noted that current treatment options for patients with advanced NSCLC included platinum based chemotherapy and/or the oral tyrosine kinase inhibitors, gefitiinb or erlotinib, for patients with NSCLC expressing activating mutations in EGFR tyrosine kinase.

3.7. The Committee noted that crizotinib is an oral inhibitor of the ALK receptor tyrosine kinase.

3.8. The Committee considered that the incidence of ALK mutations within NSCLC adenocarcinoma histology ranged from 2% to 8% with higher rates in those in younger age groups and those who have never smoked. Members considered that ALK mutation NSCLC was a subset of non-smoker lung cancers. Members noted that ALK and EGFR mutations were mutually exclusive; in that patients with ALK mutation positive NSCLC would not exhibit EGFR activating mutations and vice versa.

3.9. The Committee noted that the availability of testing for ALK mutations in New Zealand was inconsistent. Members noted that testing was available in some DHBs but some patients were paying privately for testing. Members considered that fluorescence in situ hybridization (FISH) testing was the diagnostic method of choice but immunohistochemistry (IHC) was more readily available in some centres and IHC may be used for screening prior to FISH confirmation. Members considered the current cost of ALK testing was approximately $500 per test and that this may be a significant cost for DHBs as if an ALK targeted treatment were funded it is likely all patients with NSCLC would be tested for ALK mutation.

3.10. The Committee noted that crizotinib is usually dosed at a fixed dose of 250 mg twice daily. However, members noted that bioavailability may differ depending on body weight. Members noted that crizotinib is metabolized by CYP3A4/5 so strong inhibitors or inducers of CYP3A4/5 will alter plasma concentrations. Members considered that development of resistance mutations in the ALK kinase domain and poor CNS penetration were limitations of crizotinib treatment. Members noted that the Medsafe datasheet specifies that crizotinib should be continued for as long as the patient derives benefit from treatment

3.11. The Committee noted evidence that 62% of patients experienced one of more visual impairment side effects within two weeks of initiation of therapy and that other reported common side effects include oedema (38%) and gastrointestinal events – nausea (57%), diarrhoea (49%), vomiting (45%) and constipation (38%). (Cappuzzo et al. Lung Cancer 2015;87:89-95)

First line treatment

3.12. The Committee reviewed evidence from a Phase 3, open label, randomised trial of crizotinib versus first-line pemetrexed and platinum chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in treatment naïve patients with advanced ALK-positive non-squamous NSCLC (Study A8081014 published as Solomon et al. NEJM 2014:371:2167-77). Patients were randomly assigned to received crizotinib at a dose of 250 mg twice daily or chemotherapy (pemetrexed, 500 mg per square meter of body-surface area, plus ether cisplatin, 75 mg per square meter, or carboplatin, target are under the curve of 5 to 6 mg per millilitre per minute) administered every 3 weeks for up to six cycles. Treatment was continued until RECIST-defined disease progression, development of unacceptable toxic effects, death, or withdrawal of consent. Patients in the chemotherapy group who had disease progression as confirmed by independent radiologic review could cross over to crizotinib treatment if safety screening criteria were met.

3.13. The Committee noted that 98% of the patients enrolled had stage 4 disease with only 2% having stage 3b disease. Members noted that 51% of patients were Caucasian, 46% Asian and that 63.5% were never smokers. Members noted that 94% of patients enrolled had an Eastern Cooperative Oncology Group (ECOG) score of 0-1 with the remaining patients ECOG 2. Members noted that the median duration of treatment was 10.9 months (range 0.4 to 34.3) in the crizotinib group and 4.1 months (range 0.7 to 6.2) in the chemotherapy group. Members noted that median progression-free survival, the primary endpoint of the study as assessed by independent radiologic review or death, was 10.9 months in the crizotinib treatment arm vs 7.0 months in the chemotherapy arm (Hazard Ratio (HR) 0.45; 95% confidence interval (CI), 0.35 to 0.60; p<0.001). Median overall survival (OS) was not reached in either group (HR 0.82; 95% CI, 0.54 to1.26; P=0.36) Members noted that no significant difference in OS was shown between the two arms; which the authors attributed to 70% crossover. Members considered that radiologic assessments in the clinical trial were performed more frequently that in standard clinical practice; this may have led to earlier identification of progression and crossover of treatment, and so a shorter duration of treatment, than would occur in standard clinical practice. Members noted that PFS gains in cancer did not always predict an overall survival gain therefore, in the absence for unconfounded evidence; caution was needed when extrapolating PFS gains into survival benefits for patients treated with crizotinib.

3.14. The Committee noted that pemetrexed is not currently funded in New Zealand for patients with advanced NSCLC; therefore the evidence from the Solomon study was not directly applicable to New Zealand practice. Members noted that there were no studies available directly comparing crizotinib with New Zealand standard platinum-based chemotherapy alone in a first line setting.

3.15. The Committee noted that an indirect comparison of crizotinib with non-pemetrexed platinum based chemotherapy had been provided by the supplier using a phase 3 non-inferiority study in chemotherapy naïve patients with Stage IIIB or Stage IV NSCLC comparing first-line pemetrexed/cisplatin with gemcitabine/cisplatin (Scagliotti et al. J Clin Oncol 208;26:3543-51) which showed that overall survival for cisplatin/pemetrexed was non-inferior to gemcitabine/cisplatin. Members noted that this study was previously considered by PTAC in August 2015 in relation to a previous funding application for pemetrexed. Members noted that the study populations between Solomon et al. and Scagliotti et al. were different in terms of the proportion of smokers/ex-smokers and ethnicities. Members considered the adenocarcinoma subgroup from Scagliotti et al.

was more appropriate to use for analysis. Members considered caution should be used with extrapolation of the data but that the indirect comparison did support a likely small increase in PFS gain of around 3.9 months with crizotinib treatment compared with platinum based chemotherapy in the first line setting.

Second line treatment

3.16. The Committee reviewed evidence from a Phase 3, open-label, randomised trial comparing crizotinib with single agent chemotherapy (pemetrexed or docetaxel) in patients with locally advanced or metastatic ALK-positive NSCLC that had receive one prior platinum-based regimen (Study 8081107 Shaw et al. NEJM 2013:368;25:2385-94). Members noted that median progression-free survival, the primary endpoint of the study, was 7.7 months in the crizotinib group compared with 3.0 months in the chemotherapy group (HR 0.49; 95% CI, 0.37 to 0.64; P<0.001). Members noted that there was no significant difference between the treatment groups in overall survival (HR1.02; 95% CI, 0.68 to 1.54; P=0.54). Members considered that the lack of difference in OS may have been due to treatment cross-over because the study design allowed patients in the chemotherapy group with RECIST-defined progression to cross-over to receive crizotinib.

3.17. Members noted that costs in the economic model provided by the supplier were based on median PFS instead of mean PFS which they considered would be more appropriate. Members also considered that treatment in this indication was likely to continue beyond radiologic identification of new metastases and would likely continue until patients exhibited evidence of clinical disease progression. Members considered, if funded, that patients may be more likely to have a poorer ECOG status than those included in the trials, who were mostly ECOG 0-1 given the simplicity associated with an oral therapy.

3.18. The Committee considered that the evidence for crizotinib in metastatic ALK positive NSCLC in both the first and second line settings was of medium quality and good strength however, evidence of long term efficacy was lacking and given the pricing being proposed members considered that the treatment was poorly cost effective.

4. Ibrutinib for chronic Lymphocytic leukaemia (CLL) and mantle cell lymphoma (MCL)

Application

4.1. The Committee considered an application from Janssen-Cilag Pty Ltd for the funding of ibrutinib (Imbruvica) for the treatment of patients with high risk Chronic Lymphocytic Leukaemia (CLL) (those with chromosome del(17p) or TP53 mutation at diagnosis or relapse, patients whose CLL has relapsed within 24 months of prior therapy and patients whose CLL is refractory to prior therapy (progressed within 12 months)), and patients with relapsed and/or refractory Mantle Cell Lymphoma (MCL) that has progressed within 24 months of allograft or chemotherapy or chemo-immunotherapy (rituximab-based therapy). The Committee also considered a letter from a Haematologist supporting the application for the funding of ibrutinib for patients with relapsed/refractory or TP-53 deleted CLL.

Recommendation

4.2. The Committee **recommended** that the application to fund ibrutinib for the treatment of CLL with chromosome del(17p) or TP53 mutation at diagnosis or relapse be declined.

4.3. The Committee **recommended** that the application to fund ibrutinib for the treatment of relapsed CLL (within 24 months of prior therapy) be declined.

4.4. The Committee **recommended** that the application to fund ibrutinib for the treatment of refractory CLL (progress within 12 months) be declined.

4.5. The Committee **recommended** that the application to fund ibrutinib for the treatment of relapsed and/or refractory MCL (that has progressed within 24 months of allograft or chemotherapy or chemo-immunotherapy) be listed in the Pharmaceutical Schedule with a low priority.

4.6. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee for consideration.

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

4.8. The Committee noted that CLL is the most common type of leukaemia and in New Zealand is diagnosed in 207 patients each year (Cancer NZ registrations and deaths 2011). Members noted that MCL represents about 3-10% of all Non-Hodgkin lymphomas (NHL) and that in New Zealand there were 729 registrations for NHL in 2011. Members noted that CLL and MCL are indolent diseases with variable clinical courses, and treatment is generally delayed until the patient's clinical symptoms or blood counts indicate that the disease has progressed to a point where it may affect the patient's quality of life.

4.9. The Committee noted that the incidence of TP53 mutation or 17p deletion in CLL patients ranges from 7% to 47% and that the majority of CLL patients with TP53 mutations also have 17p deletion. Members noted that in New Zealand only 17p deletion testing was routinely available. Members considered that patients with TP53 mutation or 17p deletion are part of the same CLL patient population that has significantly shortened overall survival and poorer response to therapy compared with patients with CLL without these genetic mutations.

4.10. The Committee noted that in New Zealand CLL patients with 17p deletion are not eligible for rituximab funding and that funded treatment options for these patients are FC (fludarabine and cyclophosphamide), chlorambucil, or supportive therapy. Members noted that funded treatments for CLL patients with relapsed disease or those refractory to treatment are FC, FC-R (fludarabine, cyclophosphamide and rituximab), (if they did not receive it in a first line setting), chlorambucil, or supportive therapy. Members considered that, there was an unmet health need for better treatment options for patients with 17p deletion CLL.

4.11. The Committee noted that ibrutinib is an orally administered, selective and covalent inhibitor of Bruton's tyrosine kinase (BTK) targeting B-cell malignancies. Members noted that it is registered in New Zealand for use as a single agent for the first line treatment of CLL and small lymphocytic lymphoma (SLL) who have received at least one prior therapy, or as first-line treatment in patients with CLL with 17p deletion, and in patients with MCL who have received at least one prior therapy. Members noted the ibrutinib is supplied as a 140 mg capsule and that the recommended dose is 3 capsules (420 mg) per day for the treatment of CLL and 4 capsules (560 mg) per day for the treatment of MCL.

4.12. The Committee noted the main evidence for the use of ibrutinib for the treatment of CLL was from three open-label randomised controlled trials (RESONATE, RESONATE-2 and RESONATE-17), members noted that only one of these studies had been published in a peer-reviewed journal (Byrd et al. NEJM 2014;371:213-23). Members considered that the evidence from all three trials was immature for a chronic condition, and that none of the trials used comparators relevant to the New Zealand setting. Members considered

that overall the evidence for the use of ibrutinib in the CLL indications applied for was of low strength and quality.

4.13. The Committee reviewed evidence from a phase 3, randomised, multicentre, open-label study in patients with relapsed or refractory CLL or SLL (RESONATE: Byrd et al. NEJM, 2014;371:213-23). Members noted that patients (n=391) were randomised 1:1 to receive either ibrutinib (420mg once daily) or ofatumumab (300mg in week 1 followed by 2,000 mg weekly for 7 weeks then 4 weekly for 16 weeks) until either disease progression or unacceptable toxicity with patients able to crossover to the other treatment arm following confirmed disease progression. Members noted that 31% of enrolled patients had chromosome 17p deletion and that patients in the ibrutinib group had more bulky disease (64% vs. 52%), more previous therapies (median 3 vs. 2), and a shorter time from last therapy (median 8 vs. 12 months).

4.14. The Committee noted that after a median follow-up of 9.4 months median Progression Free Survival (PFS), the primary end-point of the study, was not reached in the ibrutinib group (88% remained in PFS at 6 months) compared with a median PFS of 8.1 months in the ofatumumab group (hazard ratio (HR) for progression or death 0.22; 95% confidence interval (CI), 0.15 to 0.32; p<0.001). Members noted that at 12 months, 90% of the patients in the ibrutinib group were still alive compared with 81% in the ofatumumab group (HR 0.43; 95% CI, 0.24 – 0.79; P=0.005). Members noted that the overall response rate was 43% in the ibrutinib group compared with 4% in the ofatumumab group (odds ratio 17.4; 95% CI, 8.1 to 37.3; p<0.001). Members noted that grade ≥3 adverse events (AE) were more common in the ibrutinib group (57% vs 47%), including diarrhoea, atrial fibrillation, cataracts, infections and bleeding related events. Members noted that similar effects were observed regardless of whether patients had chromosome 17p deletion or resistance to purine analogues.

4.15. The Committee noted a poster presentation by Brown et al. (abstract 3331, American Society of Haematology 2014, Haematology/Oncology Pharmacy Association 2015) reporting an update of results of the RESONATE trial with a median follow-up of 16 months. Members noted that median PFS was not reached in the ibrutinib group vs 8.1 months in the ofatumumab group and at 12 months, 84% of patients remained in PFS in the ibrutinib group versus 18% in the ofatumumab group (HR 0.11, 95% CI 0.07 – 0.15; P<0.001). Members noted that 62% of ofatumumab participants had crossed over to the ibrutinib arm. Members noted that Brown et al. reported that patients treated with ibrutinib in earlier lines of salvage therapy experienced better outcomes than those in later lines of therapy. The overall response rate was 100% in patients treated with ibrutinib who had received 1 prior therapy (p=0.046) versus 2 (79% response) or ≥3 (78% response) prior therapies (p=0.002). Dose reductions due to an AE occurred in 6% of ibrutinib treated patients, and discontinuation due to AE or unacceptable toxicity occurred in 7% of ibrutinib treated patients.

4.16. The Committee noted that 43% of participants in the RESONATE trial had previously received treatment with bendamustine and 21% with alemtuzumab, neither of which are funded in New Zealand. Members also noted that ofatumamab is not currently funded in New Zealand and considered that the absence of evidence comparing ibrutinib with New Zealand funded comparators made it difficult to clearly quantify the benefits that patients could expect from ibrutinib treatment in the New Zealand setting. Members also considered the data to be immature, with follow-up of only 16 months, with regards to the effects on OS and PFS, and that the short term follow-up in what is a long term condition introduced further uncertainty.

4.17. The Committee reviewed evidence from a randomised, multicentre, open-label, phase 3 trial in treatment naïve patients with CLL/SLL who were 65 years of age or older (RESONATE-2: unpublished PCYC_1115-CA topline results 26 June 2015). Members noted that 269 patients were randomised to receive either ibrutinib (420mg daily) until disease progression or unacceptable toxicity, or chlorambucil (0.5mg-0.8mg) for a maximum of 12 cycles.

4.18. The Committee considered that the patient population in this trial was not directly relevant to the funding application as patients with 17p deletion were excluded. Members noted that the median duration of treatment with ibrutinib was 17.4 months (range 0.7 to 24.7 months), with 86.8% of the treatment arm continuing on ibrutinib therapy at cut-off, and median treatment duration with chlorambucil was 7.1 months (range 0.5 to 11.7 months). Members noted that median PFS, the primary endpoint of the study, was not reached in the ibrutinib arm, and was 18.9 months for the chlorambucil arm (HR 0.16, 95% CI 0.09 – 0.28, p<0.0001). Members noted that median OS was not reached in either of the treatment arms, however, ibrutinib was reported to significantly reduced the risk of death by 84% (HR=0.16, 95% CI 0.05 – 0.56, p=0.001) based on the observation that 3 deaths occurred in the ibrutinib arm versus 17 deaths in the chlorambucil arm. Members noted that overall response rate was 82.4% for the ibrutinib arm and 35.3% for the chlorambucil arm (p<0.0001). Members noted that treatment emergent adverse events were reported in 65.9% in the ibrutinib arm and grade ≥3 adverse events were reported in 35.6% of subjects treated with ibrutinib.

4.19. The Committee reviewed evidence from an open label, single arm, study of ibrutinib (420mg daily until progression) in 144 patients with del(17p) CLL who had failed at least one previous therapy (RESONATE-17: O'Brien et al. ASH 2014 abstract). Members noted that participants had a median age of 64 years, and had received a median of 2 previous therapies, Members noted that 21% of participants had received previous treatment with alemtuzumab, which is not currently funded in New Zealand for patients with CLL. Members noted that, after a median follow-up of 11.5 months, 65% of patients had a treatment response and at 12 months 79.3% were still alive. Members considered that because this study was non-randomized it was not possible to determine with certainty the magnitude of the potential benefits of ibrutinib within the New Zealand context.

4.20. The Committee also reviewed evidence for ibruitinib in the treatment of CLL from a number of other open label non-randomised single arm Phase 1b-2 studies.

4.21. The Committee noted that the currently funded treatment options for patients with MCL in New Zealand included R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone) or chlorambucil with steroids. Members noted that MCL generally has rapid progression, a high rate of relapse after initial treatment, and a median survival time of approximately 3 years. Members noted that there is limited evidence about the efficacy of treatment for MCL and considered that MCL patients who relapse or are refractory following treatment have limited effective treatment options in the current New Zealand setting.

4.22. The Committee reviewed data from an unpublished open label randomised phase 3 trial comparing ibrutinib (560mg daily until disease progression) with temsirolimus (175mg IV day 1,8,15 of first 21 day cycle, then 75mg IV day 1,8,15 until disease progression) in 280 patients with relapsed (70%) or refractory (30%) MCL (RAY (PCI-32765MCL3001). Members noted that all patients had received at least one prior rituximab-containing treatment regime, with a median of 2 previous lines of treatment. Members noted that median duration of treatment was 14.4 months in the ibrutinib arm and 3.0 months in the temsirolimus arm.

4.23. The Committee noted that after a median follow-up of 20 months, median PFS, the primary endpoint of the study, was 14.6 months in the ibrutinib arm compared with 3.2 months in the temsirolimus arm (HR=0.43, CI 0.32-0.58, p<0.0001) and 59 (42.4%) ibrutinib patients had died compared with 63 (44.7%) temsirolimus patients (HR=0.76, 95% CI 0.53-1.09, p=0.1324). The Committee reviewed evidence from a phase 2, open label, single arm study of ibrutinib (560mg daily) for the treatment of patients with relapsed or refractory MCL (Wang et al. NEJM 2013;369:507-16). Members noted that the study enrolled patients who had received at least one but no more than five previous lines of treatment, with no partial or better response to the most recent treatment

regimen or with disease progression after the most recent regimen. Members noted that patients had received a median of 3 previous treatments, 43% had previous been treated with bortezomib, which is not funded in New Zealand for MCL, and 86% of patients had intermediate risk or high risk disease. Members noted following a median follow-up period of 15.3 months overall response rate, the primary endpoint of the study, was 68% (comprising 21% complete response and 47% partial response) and that prior treatment with bortezomib had no effect on response rate. Members noted that the estimated median PFS was 13.9 months (range, 0.7 – 21.4; 95% CI, 7.0 to not reached), median OS was not reached, the estimated rate of overall survival was 58% at 18 months.

4.24. The Committee noted a poster presentation by Wang et al. (Poster ASH 2014, Blood 2015;126:739-45) reporting long term follow up of patients in this study. Members noted that at a median follow-up of 26.7 months, the median duration of response was 17.5 months (95% CI 14.9- not estimable (NE)), median PFS was 13 months (95% CI 7.0-17.5) and a median OS was 22.5 months (95% CI 13.7-NE).

4.25. The Committee considered that the evidence for the use of ibrutinib in the treatment of MCL in terms of OS remains immature and that due to the non-randomised study designs that there remained uncertainty regarding the magnitude of the potential benefit of ibrutinib for the treatment of MCL in the New Zealand population. Members considered that despite this uncertainty ibrutinib may be beneficial as an alternative treatment option for patients with MCL due to the aggressive course of this disease and poor prognosis with currently funded treatment options.

4.26. The Committee considered that in general the patient population and treatment pathways for ibrutinib, and other new therapies, were developing and not well defined for either CLL or MCL at this time. However, members considered that, despite uncertainty of clinical benefit, ibrutinib is likely to provide advantages over the currently funded treatments for CLL and MCL due to its oral method of delivery and its moderate toxicity profile. The Committee considered that there remains considerable uncertainty about the benefits that ibrutinib may bring in a New Zealand setting as the studies have either compared ibrutinib to treatments that are not currently funded in New Zealand, or have selected populations that are neither relevant nor generalizable to the target population in New Zealand. The Committee also considered that much of the evidence for ibrutinib is from immature and unpublished studies, and that long term survival data cannot be determined based on currently available evidence. Members considered that at the current price being proposed the cost effectiveness of ibrutinib for the treatment of CLL and MCL was unacceptably high.

4.27. The Committee also considered that the fiscal risks associated with listing ibrutinib are likely to be large as there is considerable uncertainty relating to the benefits of treatment and treatment duration. Members considered that a Special Authority criteria could be developed to target this treatment to patients who would benefit most and that [redacted]

4.28. The Committee noted and agreed with the July 2015 Pharmaceutical Benefits Advisory Committee (Australia) Outcomes paper which did not recommend that ibrutinib be listed for the treatment of relapsed or refractory CLL and SLL as 'the patient population and clinical place of ibrutinib were not adequately defined, the size of the comparative benefit could not be quantified, and the cost effectiveness and financial implications were underestimated and unacceptably high.'

4.29. The Committee considered that the application should be reviewed by the Cancer Treatments Subcommittee for further advice regarding the place in therapy for ibrutinib and its expected risks and benefits compared with currently funded treatment options in New Zealand.

5. Rituximab for Hairy Cell Leukaemia

Application

5.1. The Committee considered an application from a clinician for the funding of rituximab (Mabthera) for patients with CD20+ hairy cell leukaemia (HCL) requiring treatment including patients with: residual disease or relapsed disease after purine analogue therapy, those ineligible for purine analogue therapy, or with hairy cell leukaemia variant (HCLv).

Recommendation

5.2. The Committee **recommended** that rituximab be funded for patients with CD20+ HCL with a medium priority.

5.3. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee for consideration.

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

Discussion

5.5. The Committee noted that HCL is an uncommon CD20+ indolent B cell malignancy that presents in either classic or variant form with an incidence of approximately 16 patients per year in New Zealand. Members noted that many HCL patients are asymptomatic for months or years after diagnosis and that treatment is initiated only once symptoms develop. Members also noted that HCLv is a more aggressive and less treatment responsive disease than classic HCL.

5.6. The Committee considered that HCL patients currently have limited funded treatment options noting that either cladribine, pentostatin or interferon treatment are used in both first-line and relapsed or refractory settings and noted although the majority of HCL patients may initially have a good response to these agents, that with repeated retreatment, as is the current practice, reduced response rates, durability of response and increased toxicity is generally seen. Members also noted that some HCL patients are refractory or ineligible for purine analogue treatment and considered there was an unmet health need in these populations.

5.7. The Committee noted that rituximab is used to treat other CD20 mediated pathologies and is funded for the treatment of B-cell lymphoproliferative disorders after transplant, indolent low grade Non-Hodgkin's Lymphoma (NHL), aggressive CD20 positive NHL, and Chronic Lymphocytic Leukaemia for patients who meet the Special Authority (SA) criteria. Members noted that although rituximab was not currently funded for HCL the current SA criteria for indolent NHL may be interpreted by some clinicians to include HCL and noted that PHARMAC may be interested in clarifying the wording of this SA criterion. Members noted that HCL is not a Medsafe approved indication for rituximab, and would unlikely to be registered by the supplier due to the small patient numbers.

5.8. The Committee reviewed a number of studies to support the use of rituximab as monotherapy or in combination with purine analogues in the treatment of HCL and HCLv in first-line and relapsed or refractory settings:

- Ravandi et al. Blood 2011;118:3818-23 – a phase 2 study of cladribine (5.6 mg/m2 daily for 5 days) one month later followed by rituximab (375 mg/m2 per dose weekly for eight weeks) in 36 patients with newly diagnosed classic HCL and untreated

HCLv. Members noted that 44% had persistent disease following cladribine and 100% had a complete response (CR) after treatment with rituximab (n=36). Members noted 33% had grade 3 or 4 infections (shingles, cellulitis, neutropenic fever).

- Le Clerc et al. Ann Haem 2014;94:89-95 – a retrospective, non-randomised study of rituximab (375 mg/m2, several treatment sequences) as monotherapy or in combination with other treatments (cladribine, pentostatin, interferon, steroids) in 41 patients with HCL in first line or relapsed settings. Members noted that a complete haematological response (CHR) was achieved in all patients that received first-line treatment irrespective of whether it was given as monotherapy or in combination. Members noted that in relapsed settings CHR was observed in 86% of patients when given in combination and 54% when given as monotherapy. Members noted there was no association between the number of rituximab treatments and the probability of response to treatment.

- Thomas et al. Blood 2003;102:3906-11 – a prospective non-randomised, study of rituximab (375 mg/m2 per dose weekly for eight weeks) in 15 patients with relapsed or refractory active HCL following prior treatment with purine analogues (cladribine or pentostatin) or interferon. Members noted that there were no HCLv patients included in this study, and that after follow up of 32 weeks the overall response rate was 80% (n=12), with 53% of patients (n=8) achieving a complete response.

- Lauria et al. Haematologica 2000;86:1046-50 – a non-randomised study of 10 patients with relapsed HCL treated with rituximab monotherapy (375 mg/m2 once a week for 4 weeks) following previous treatment with purine analogue. Members noted that after follow up of 16 months, 1 patient had CR, 4 a partial response (PR), 3 a minor response and 2 patients had no response. Members also noted that treatment appeared to be well tolerated with no grade 3 – 4 toxicity observed, and no infections or haemorrhagic complications.

- Else et al. Leuk & Lymph 2011;52(Suppl 2);75-8 – a retrospective review of rituximab treatment (375 mg/m2 per dose) in combination with PA (cladribine or pentostatin) in patients with relapsed HCL (n=18) who had previously been treated with one or more lines of single agent cladribine or pentostatin. Members noted the study did not include HCLv patients, and that patients previous treatment regimens were heterogenous as were the study treatment regimens; fourteen patients received rituximab in combination with a purine analogue, while four patients received rituximab as a sequential therapy following 1-2 months of purine analogue therapy and rituximab was given for between four and eight doses. Members noted that after 36 months of follow up (5-83 months) the 16 patients that obtained complete response (CR) remained in CR and the remaining 2 patients obtained a partial response. Members noted the estimated recurrence rate of 7% in year one, 21% in year two and 42% in year three.

- Gerrie et al. Blood 2012;119:1988-91 – a retrospective analysis of patients treated with rituximab (375 mg/m2 intravenously every 28 days) in combination with fludarabine (40mg/m2 per day orally on days 1-5) in relapsed/refractory HCL after first line treatment with cladribine (n=3) or multiple lines of therapy (n=12). Members noted that patients underwent a median of 4 cycles of treatment (range 2-4). Members noted that not all participants had a full data set but from the response data that was available 13 patients achieved normalisation of peripheral blood counts, an absence of circulating hairy cells, and resolution of splenomegaly if initially present. Members noted that 14 patients were progression free without further therapy after a median follow up of 35 months (10-80 months) with one patient developing recurrence at 31 months, and a 5 year PFS of 89% and 83% 5 year overall survival.

- Cervetti et al. Br J Haem 2008;143:294-303 – a non-randomised study of rituximab (375 mg/m2 once a week for four weeks) after cladribine (5 mg/m2 either weekly for six weeks or 5 mg/m2 daily for 5 days) for partial response or persistent minimal residual disease in 27 patients. Members noted that the five year PFS was 83%, independent of age, bone marrow response to cladribine but dependent on quality of response to cladribine, with two year PFS 50% for patients achieving PR compared with 94% for cases in CR ($p<0.001$).

- Krietman et al. Clin Canc Res 2013;19:6873-80 – non-randomised studies of the use of rituximab (375 mg/m2 per dose weekly for eight weeks) as monotherapy or in combination with cladribine (0.15mg/kg per day for 5 days) in the treatment of patients with HCLv in both first line and relapsed or refractory settings. Members noted that Kreitman et al. reported 90% of patients achieved CR when treated with rituximab in combination with cladribine compared with 8% of patients treated with cladribine alone.

- Roback, Leuk Lymph 2011;52(Suppl 2):53-6 – a review of HCLv management in 100 patients treated with splenectomy, cladribine, pentostatin, fludarabine, interferon alpha, rituximab, alemtuzumab and BL22.

5.9. The Committee considered the evidence for the use of rituximab for the treatment of HCL and HCLv was limited and of low quality, being mainly from small, and often retrospective, case series but reported favourable responses with minimal toxicity. Members considered that because HCL is an uncommon condition, it is unlikely that any large randomised controlled trials would be conducted in the future.

5.10. The Committee noted that the number of cycles of rituximab given to patients in the studies presented ranged from two to eight cycles and considered that although there was uncertainty regarding the optimal number of cycles it was likely that 4-6 cycles of treatment would be appropriate. Members considered that optimal dosing may vary between HCL and HCLv patients.

5.11. The Committee considered that rituximab would likely be used in combination with purine analogues as it appeared to result in improved efficacy but noted that rituximab may be used as monotherapy for patients who are intolerant or ineligible for purine analogues.

5.12. The Committee considered that the currently available evidence indicated the addition of rituximab to the treatment paradigm for HCL patients would likely provide additional health gains when compared to current treatment options and would likely reduce the need for purine analogue treatments and extend the interval between retreatments. However, members considered that from the currently available evidence the position of rituximab within the treatment paradigm and the appropriate duration of treatment for both HCL and HCLv was uncertain. Members recommended the application should be referred to the Cancer Treatments Subcommittee for consideration.

6. Cinacalcet (Sensipar) in patients with parathyroid disorders

Application

6.1. The Committee considered the funding of cinacalcet on the Pharmaceutical Schedule for patients with parathyroid disorders.

Recommendation

6.2. The Committee **recommended** that funding of cinacalcet on the Pharmaceutical Schedule for non-malignant parathyroid disorders (any cause) without symptomatic hypercalcaemia be declined.

6.3. The Committee **recommended** that the funding of cinacalcet on the Pharmaceutical Schedule for patients with non-malignant secondary hyperparathyroidism with or without elevated serum calcium, except in the limited setting of calciphylaxis after other treatments have been tried and failed, be declined.

6.4. The Committee **recommended** that the funding of cinacalcet on the Pharmaceutical Schedule in patients with tertiary hyperparathyroidism and elevated serum calcium be declined.

6.5. The Committee **recommended** that the funding of cinacalcet on the Pharmaceutical Schedule in patients with primary hyperparathyroidism and elevated serum calcium who do not have an absolute contraindication for parathyroid surgery be declined.

6.6. The Committee **recommended** that cinacalcet be funded on the Pharmaceutical Schedule in hospitals and community for patients with parathyroid carcinoma with symptomatic hypercalcaemia unresponsive to other treatments subject to the following Special Authority criteria/hospital restrictions with a medium priority:

Initial application – only from a nephrologist or endocrinologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. The patient has been diagnosed with a parathyroid carcinoma; and
2. The patient has persistent hypercalcaemia (serum calcium ≥3 mmol/L) despite previous first-line treatments including bisphosphonates and sodium thiosulfate; and
3. The patient is symptomatic.

Renewal application – only from a nephrologist or endocrinologist. Approvals valid without further renewal unless notified for applications meeting the following criteria:
Both:

1. The patient's serum calcium level has fallen to < 3mmol/L; and
2. The patient has experienced clinically significant symptom improvement.

6.7. The Committee **recommended** that cinacalcet be funded on the Pharmaceutical Schedule in hospitals and community for patients with symptomatic calciphylaxis only after failure of bisphosphonates and sodium thiosulfate subject to the following Special Authority criteria/hospital restrictions with a medium priority

Initial application – only from a nephrologist or endocrinologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. The patient has been diagnosed with calciphylaxis (calcific uraemic arteriolopathy); and
2. The patient has symptomatic (e.g. painful skin ulcers) hypercalcaemia (serum calcium ≥3 mmol/L); and
3. The patient's condition has not responded to previous first-line treatments including bisphosphonates and sodium thiosulfate.

Renewal application – only from a nephrologist or endocrinologist. Approvals valid without further renewal unless notified for applications meeting the following criteria:
Both:

1. The patient's serum calcium level has fallen to < 3mmol/L; and
2. The patient has experienced clinically significant symptom improvement.

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

Discussion

6.9. The Committee noted that it had previously reviewed the funding of cinacalcet for treatment of elevated calcium levels in patients with parathyroid disorders, most recently in February 2015. The Committee noted it had previously considered that the available evidence did not support a benefit of cinacalcet in terms of patient relevant endpoints such as improving cardiovascular outcomes or reducing severe bone pain in patients with secondary hyperparathyroidism.

6.10. The Committee noted that since its February 2015 review additional advice had been sought from members of the Endocrinology Subcommittee, which had provided two further studies for consideration:

- A phase III double-blind, multi-centre, randomised, placebo-controlled study of cinacalcet given for 28 weeks or less in patients with asymptomatic primary hyperparathyroidism unable to undergo parathyroidectomy (Khan et al. Eur J Endocrinol 2015;172:527-35). The study found that cinacalcet was significantly more effective than placebo at normalising serum calcium in this patient population. The Committee noted that the study did not evaluate changes in bone mineral density, fracture outcomes or cardiovascular outcomes, which would have been useful.

- A secondary analysis of the EVOLVE trial looking at reductions in serum fibroblast growth factor-23 (FGF23) (Moe et al. Circulation 2015;132:27-39). The EVOLVE trial was a randomised clinical trial comparing cinacalcet to placebo in addition to conventional therapy (phosphate binders/vitamin D) in 3883 patients receiving hemodialysis with secondary hyperparathyroidism (EVOLVE Trial Investigators, Chertow et al. N Engl J Med 2012;367:2482-92), which reported that cinacalcet did not significantly reduce the risk of death or major cardiovascular events in this patient group. The secondary analysis reported that cinacalcet was significantly more effective than placebo at lowering serum FGF23. Among patients randomised to cinacalcet, a ≥30% reduction in FGF23 between baseline and week 20 was associated with a nominally significant reduction in the primary composite end point (relative hazard (HR), 0.82; 95% confidence interval, 0.69-0.98), cardiovascular mortality (HR 0.66, 95% CI 0.50-0.87), sudden cardiac death (HR 0.57 (0.37-0.86)), and heart failure (HR 0.69 (0.48-0.99)). The Committee noted that this secondary analysis may be subject to Type I error rate inflation through multiple statistical testing so that it was very difficult to interpret these selected positive findings, albeit that they were statistically significant, with wide confidence intervals in the context of an overall negative main study. The Committee was also uncertain of the clinical relevance of the finding of an association between cincalcet use with changes in FGF23.

6.11. The Committee noted that applications for cinacalcet through the Named Patient Pharmaceutical Assessment (NPPA) pathway were increasing, to the extent that PHARMAC staff considered that the Pharmaceutical Schedule was a more appropriate pathway to consider funding of cinacalcet, in accordance with principle three of the NPPA Policy ("The NPPA Policy is designed for individual assessment"). As such, PHARMAC staff sought review of funding recommendations from PTAC for a range of potential indications for cinacalcet.

Primary hyperparathyroidism

6.12. The Committee considered that the most effective treatment for primary hyperthyroidism is parathyroidectomy and, as such, cinacalcet should not be funded for patients who are able to undergo a parathyroidectomy.

6.13. The Committee noted that there was a small group of patients with an absolute contraindication to parathyroidectomy surgery. The Committee considered that the best available evidence for cinacalcet in patients with primary hyperthyroidism unable to undergo parathyroidectomy surgery comes from the Khan et al. (2015) trial outlined

above. However, the Committee noted a lack of evidence for clinically important outcomes from cinacalcet treatment in this patient group e.g. symptom reduction, reduction in cardiovascular outcomes and so that at present there appeared to be insufficiently strong evidence on which to make a positive funding recommendation for listing on the Pharmaceutical Schedule. The Committee noted that the definition of contraindication to parathyroidectomy surgery was potentially open to interpretation, and considered that documentation of contraindication to surgery from an experienced head and neck surgeon in a centre where parathyroidectomies are commonly performed would ensure consistency of defining the patient group.

6.14. The Committee considered that for patients with primary hyperparathyroidism, with contraindications for surgery, but who did not have symptomatic hypercalcaemic, that cincalcet use should be declined.

Secondary hyperparathyroidism

6.15. Overall, the Committee considered that, taking into account previous reviews and Subcommittee advice, the available body of evidence supported the efficacy of cinacalcet in reducing serum calcium in secondary hyperparathyroidism. However, the Committee also noted that cinacalcet use in this setting was not associated with improvement in cardiovascular outcomes. The Committee considered that evidence for benefit on other clinically meaningful outcomes such as bone pain and fracture risk, was generally poor or lacking. Therefore, the Committee considered that cinacalcet should not be funded for this indication.

Tertiary hyperparathyroidism

6.16. The Committee noted that tertiary hyperparathyroidism occurs in patients with long-standing secondary hyperparathyroidism, almost always in the setting of chronic renal failure, and reflects development of autonomous (unregulated) parathyroid function following a period of persistent parathyroid stimulation. As the parathyroid gland is essentially resistant to calcium concentrations in patients with tertiary hyperparathyroidism, the Committee noted that there appeared to be little pathophysiological rationale for the use of cinacalcet in this indication. Further, the clinical evidence for benefit with use in patients with tertiary hyperparathyroidism was lacking. Therefore, the Committee considered that cinacalcet should not be funded for this indication.

Parathyroid Malignancies

6.17. The Committee considered that there was modest evidence from cohort studies that it would be reasonable for a trial of cinacalcet in patients with parathyroid carcinomas with symptomatic hypercalcaemia unresponsive to other treatments including bisphosphonates and sodium thiosulfate. The Committee considered that this would be only a very small number of patients, potentially less than 10 per year.

Calciphylaxis

6.18. The Committee noted that cinacalcet is not registered for use in calciphylaxis (calcific uraemic arteriolopathy), although this does often occur alongside hyperparathyroidism. The Committee considered that the evidence for use of cinacalcet in the treatment of calciphylaxis unrelated to hyperparathyroidism was sparse and anecdotal, consisting primarily of case reports (eg Mohammed. Nephrol Dial Transplant 2008;23:387-9; Robinson et al. Arch Dermatol 2007;143:152-4).

6.19. However, the Committee considered that for patients with symptomatic calciphylaxis, usually manifested by conditions such as painful skin ulcers, then it was supportive of cinacalcet use only after failure of other therapies including bisphosphonates and sodium thiosulphate.

General remarks

6.20. The Committee noted that cinacalcet had been removed from the Pharmaceutical Benefits Scheme in Australia in August 2015, on the basis of unacceptably poor cost effectiveness. The Committee considered it could be useful to contact the Endocrine Society of Australia for information on how the delisting was managed.

6.21. The Committee considered that there was no biological rationale, or evidence, for the use of cinacalcet in patients with parathyroid disorders (any cause) without hypercalcaemia and, therefore, cinacalcet should not be funded in this patient group.

6.22. The Committee considered that for any indication in which cinacalcet funding was sought, the patient should have symptoms of hypercalcaemia such as important cognitive changes and should have had a trial of other appropriate first-line treatments including bisphosphonates and sodium thiosulfate, and ongoing funding of cinacalcet should require evidence of serum calcium reduction and evidence of clinically significant symptom improvement.

7. Idarucizumab for dabigatran reversal

Application

7.1. The Committee considered an application from Boehringer Ingelheim regarding the funding of idarucizumab (Praxbind) in Section H of the Pharmaceutical Schedule for dabigatran reversal.

Recommendation

7.2. The Committee **recommended** that idarucizumab be listed in Section H of the Pharmaceutical Schedule for the specific reversal of the anticoagulant effects of dabigatran when required in situations of life-threatening or uncontrolled bleeding, or for emergency surgery or urgent procedures, with a medium priority.

7.3. 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 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 although idarucizumab is still currently being evaluated by Medsafe registration in New Zealand, the proposed indication is for use in patients treated with dabigatran when rapid reversal of the anticoagulant effects of dabigatran is required in life-threatening or uncontrolled bleeding, or for emergency surgery/urgent procedures.

7.5. The Committee noted idarucizumab is a humanised mouse monoclonal antibody fragment supplied as two 50 mL vials each containing 2.5 g idarucizumab solution for injection/infusion. Idarucizumab has an affinity for dabigatran 300 times greater than the affinity of dabigatran for thrombin. In therapeutic doses, idarucizumab binds both free and thrombin-bound dabigatran, with the resulting dabigatran-idarucizumab complex being excreted via the kidneys.

7.6. The Committee noted that dabigatran is a direct thrombin inhibitor used in the prevention and treatment of deep vein thrombosis and pulmonary embolism, and for the prevention of stroke and thromboembolic events in non-valvular atrial fibrillation. Peak plasma levels are reached after 0.5-2 hours, with a half-life following multiple doses of

about 12-14 hours. The volume of distribution of dabigatran is 60-70L indicating moderate tissue distribution. Renal excretion is the major elimination pathway, leading to a prolonged half-life with renal (if CrCl < 30 ml/min, then half-life 22-35 hours).

7.7. The Committee reviewed a graph plotting monthly patient numbers being dispensed dabigatran and warfarin since the listing of dabigatran in July 2011. The Committee noted a steady increase in the number of patients taking dabigatran over time, with the number of patients taking dabigatran now exceeding the number taking warfarin. Members felt that patient numbers would continue to grow given the increasing emphasis on reducing the number of preventable strokes.

7.8. The Committee noted that no data is available comparing rates or outcomes of dabigatran associated major bleeding events in Maori and Pacific peoples when compared with other ethnic groups. The Committee noted age-specific three year cumulative incidence of dabigatran dispensing by ethnicity sourced from PHARMAC data and noted that dabigatran prescribing was higher in in Maori than other ethnic groups, likely due to the higher rates of atrial fibrillation in this group.

7.9. The Committee noted bleeding is the most clinically relevant adverse effect of dabigatran. Between July 2011 and September 2015, the Centre for Adverse Reactions Monitoring (CARM) received a total of 710 adverse reaction reports for dabigatran. Of these 710 reports, 304 patients experienced a bleeding event, with 189 of these bleeding events being classified as serious.

7.10. The Committee considered the content of the Guidelines for testing and perioperative management of dabigatran and the Guidelines for management of bleeding with dabigatran. The Committee noted that these guidelines have been developed by PHARMAC utilising expert clinical opinion, including a recent review by the Haematology Subcommittee of PTAC during its October 2014 meeting. A Member considered that the measures outlined in these Guidelines have some practical shortcomings. The Member noted that tranexamic acid is not particularly effective during acute bleeding events, that oral charcoal is not recommended immediately prior to anaesthesia, and that dialysis can be time consuming and may not be available for acute use in all hospitals. Incomplete removal of dabigatran with dialysis is also a potential problem. Prothrombin complex concentrates were thought to be moderately effective in reversing life-threatening bleeding. Activated prothrombin complex concentrates products such as Factor VIII inhibitor bypassing fraction were deemed to be effective, but came at a considerable cost and have been associated with the development of serious thrombotic adverse events.

7.11. The Committee reviewed the bleeding outcomes reported in the RE-LY trial of dabigatran in atrial fibrillation by Connolly et al. and subsequent amendments (N Engl J Med. 2009;361:1139-51, N Engl J Med. 2010;363:1875-6, N Engl J Med. 2014;371:1464-5). The Committee noted the annual incidence rates of major bleeding for dabigatran were 2.92% and 3.40% for dabigatran 110 mg and 150 mg twice daily respectively. The Committee also noted the annual rates of life-threatening bleeding for dabigatran were 1.27% and 1.52% for dabigatran 110 mg and 150 mg twice daily respectively. These bleeding rates for dabigatran were lower than those observed in the warfarin group. The Committee noted the annual incidence rate of major bleeding from other large Phase 3 dabigatran trials varied from 0.6% to 3.32%.

7.12. The Committee noted the view of Makris and colleagues (Br J Haematol. 2013;160:35-46), who considered that the bleeding event outcomes in the RE-LY trail are likely to be conservative when compared with the general population, as this trial excluded many patients with extreme body weights, significant renal impairment and multiple co-morbidities.

7.13. The Committee considered that the incidence of bleeding episodes requiring admission to hospital and consequent administration of idarucizumab was likely underestimated in

the supplier's submission. The Committee felt that while there were a number of uncertainties in predicting this rate, annual rates of usage were more likely to lie between the supplier's estimate of [redacted] and the 3.40% incidence of major bleeding in the RE-LY trial (150 mg twice daily group). Idarucizumab usage would most likely increase over time with increased dabigatran usage and increased familiarity with a wider group of clinicians.

7.14. Members considered that dabigatran[1], if funded, would be used as monotherapy or with tranexamic acid (and in conjunction with best supportive care including blood products) for the vast majority of bleeding events in dabigatran treated patients presenting in emergency departments.

7.15. The Committee reviewed an interim analysis by Pollack et al. (N Engl J Med. 2015;373:511- 20) of the first 90 patients in the RE-VERSE AD phase-III multinational prospective open-label cohort study. The RE-VERSE AD trial is a non-randomised prospective cohort study evaluating the efficacy and safety of 5g intravenous idarucizumab in adult patients who have serious bleeding (group A) or require an urgent procedure (group B). The Committee noted a high frequency of renal impairment and comorbidities amongst participants, and that the median time since last dabigatran dose was 15.4 hours. The RE-VERSE AD study remains ongoing with the investigators intending to recruit up to 300 patients at more than 400 centres in 38 countries. The Committee noted that 30 patients from New Zealand have been included in the interim analysis.

7.16. The Committee noted RE-VERSE AD's primary end point is the maximum percentage reversal of the anticoagulant effect of dabigatran, as determined at any point from the end of the first idarucizumab infusion to 4 hours after the second infusion, with the percentage reversal assessed on the basis of the measurement of the dilute thrombin time (dTT) or ecarin clotting time (ECT) at a central laboratory. Secondary end points as assessed by the treating clinician are bleeding severity (ISTH, GUSTO), reduction/cessation in bleeding in group A, hemodynamic stability in group B, and ICH outcome at 90 days.

7.17. The Committee noted that 68 of the 90 patients who received idarucizumab as part of RE-VERSE so far had an elevated dTT, and 81 had an elevated ECT at baseline. Patients with normal dTT and ECT were excluded from the efficacy analysis. A Member noted that at their DHB Hospital that these blood results would take at least 20 minutes to become available to the treating clinician. The Committee considered it would be clinically unreasonable to delay reversal while awaiting these results if the bleeding presentation was clinically significant or potentially life-threating.

7.18. The Committee noted that if listed, idarucizumab would primarily be used within hospital emergency departments, operating theatres and intensive care units.

7.19. The Committee noted that idarucizumab could be stored in the blood bank and only available for use with haematologist approval, however the Committee considered it clinically unreasonable to delay reversal while the drug was transferred from the blood bank or haematologist approval was sought in the case of potentially life-threating haemorrhage.

7.20. The Committee noted that following idarucizumab administration, dTT was normalized within minutes of infusion in 98% of the patients in group A who could be evaluated and in 93% of those in group B who could be evaluated. The ECT was normalized within minutes of infusion in 89% and 88% of the patients who could be evaluated, respectively. The median maximum percentage reversal in both groups was 100% and

[1] Typographical error – incorrectly stated as dabigatran; correct pharmaceutical is idarucizumab. This will be corrected at the February 2016 PTAC meeting.

reversal was evident after a 2.5 g dose of idarucizumab. Among 35 patients in group A, who could be assessed, haemostasis, as determined by local investigators, was restored at a median of 11.4 hours. Among 36 patients in group B who underwent a procedure, normal intraoperative haemostasis was reported in 33, and mildly or moderately abnormal haemostasis was reported in 2 patients and 1 patient, respectively.

7.21. The Committee noted that at 12 hours and 24 hours, the dTT was below the upper limit of the normal range in 90 percent of the patients in group A and in 81 percent of those in group B, and the ECT was below the upper limit of the normal range in 72 and 54 percent, respectively. The Committee considered it was likely that some patients will require additional doses of idarucizumab to maintain reversal after 12 hours, especially in patients with renal impairment.

7.22. The Committee noted the contents of the 4-month safety update report for RE-VERSE AD provided as part of the submission. [redacted] Members noted that there was an unknown but potentially significant concern surrounding antibody development. Neutralising antibody development may reduce efficacy if required for another subsequent event at a later date.

7.23. Members felt that a reversal agent was clinically necessary for life-threatening bleeding such as intracranial haemorrhage or for emergency surgery, but Members expressed concerns about the potential for 'convenience usage' prior to less urgent surgery or procedures. Members considered that there was also likely to be significant usage for various presentations of apparent bleeding that may be later deemed to have been unnecessary once laboratory results become available.

7.24. Members considered it reasonable to suggest that the use of idarucizumab may result in some reduction in duration of hospital stay, duration of intensive care unit stay, usage of blood products and prothrombin complex concentrates and emergency surgery to correct bleeding; although due to the lack of a comparison arm in the RE-VERSE AD trial, these potential benefits are difficult to quantify.

7.25. Overall, the Committee considered that the evidence provided in the RE-VERSE AD trial for idarucizumab and its reversal of the anticoagulant effects of dabigatran when required in life-threatening or uncontrolled bleeding or for emergency surgery/urgent procedures was of moderate quality. Members had a high level of confidence that idarucizumab is an effective reversal agent for dabigatran; however Members expressed concern that due to the limitations in study design, the clinical benefits of reversal compared with the currently funded treatments were difficult to establish.

8. Omalizumab for chronic spontaneous urticaria

Application

8.1. The Committee reviewed an application from a clinician for widening access to Omalizumab for the treatment of severe urticaria.

Recommendation

8.2. The Committee **recommended** access to omalizumab be widened to include the treatment of severe spontaneous urticaria with a low priority and recommended the

Dermatology Subcommittee review the application to recommend appropriate Special Authority criteria.

8.3. 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vii) The direct cost to health service users.*

Discussion

8.4. The Committee noted that urticaria is a common disorder but that between 1 and 2% of the population experience chronic urticaria that lasts for a period of over six weeks. The Committee noted that there were two forms of urticaria – inducible chronic urticaria defined as physical, cholinergic, contact or aquagenic urticaria and chronic spontaneous urticaria where patients present with the spontaneous onset of wheals and/or angioedema for more than 6 weeks. The application is for the treatment of the chronic spontaneous form of urticaria.

8.5. The Committee noted that treatment included antihistamines (up to a dose 4 times the recommended dose), ciclosporin, leukotriene inhibitors, phototherapy; and 4th line treatment including prednisone, sulfasalazine, methotrexate, anti-TNF biologics and intravenous immunoglobulin among others.

8.6. The Committee noted the disease activity is measured by the Urticaria Activity Score (UAS) which measures the number of wheals, the intensity of the itch and the length of time and Quality of Life measurements assessed by the Chronic Urticaria Quality of Life (CU-Q2oL) questionnaire, Angioedema Quality of life (AE-QoL) or the Dermatology Life Quality Index (DLQI).

8.7. The Committee noted that omalizumab is a humanised, recombinant, immunoglobulin G (IgG) monoclonal antibody that binds to immunoglobulin E (IgE) and prevents it from binding to its high-affinity receptor on mast cells and basophils, thereby reducing IgE-induced mast cell and basophil degranulation and the subsequent release of histamine. Omalizumab is indicated for the treatment of allergic asthma and chronic idiopathic urticaria and is currently listed in the Pharmaceutical Schedule for the treatment of severe, life threatening asthma.

8.8. The Committee noted that the key clinical trial evidence to support the use of omalizumab for the treatment of severe chronic urticaria comes from three clinical trials – ASTERIA I (Saini et al; J Invest Dermatol. 2015;135:67-75), ASTERIA II (Maurer et al; N Engl J Med 2013;368:924-35), and GLACIAL (Kaplan et al; J Allergy Clin Immunol 2013; 132:101-9).

- ASTERIA I enrolled 319 adult and adolescent patients in a randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of subcutaneous omalizumab as add-on therapy for 24 weeks in patients with chronic idiopathic urticaria/spontaneous urticaria who remained symptomatic despite H_1 antihistamine treatment at licensed doses. Patients were randomised to placebo, or omalizumab at doses of 75mg, 150 mg and 300 mg every four weeks.

- ASTERIA II enrolled 323 adult and adolescent patients in an international, multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of subcutaneous omalizumab over 28 weeks in the treatment of patients with chronic idiopathic urticaria who had remained symptomatic despite the use of approved doses of H_1 antihistamines. Patients were randomised to receive three subcutaneous injections of 75mg, 150 mg and 300 mg omalizumab or placebo.

- GLACIAL enrolled 336 adult and adolescent patients in a multicentre, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety and tolerability of subcutaneous 300 mg omalizumab in patients with chronic idiopathic urticaria/spontaneous urticaria who remained symptomatic despite treatment with H_1 antihistamines at up to 4 times the approved dose plus H_2-antihistamines, leukotriene inhibitors, or both over a period of 24 weeks.

8.9. The Committee noted that the 150 mg and 300 mg doses of omalizumab were statistically superior to placebo for improvement in UAS7, Weekly Itch Severity Score (WISS) and the Weekly Number of Hives Score (WNHS) in all three studies. The committee noted that, with the exception of the omalizumab 300 mg group in the ASTERIA I trial (P=0.0062), differences in change from baseline in EQ-5D index scores between the omalizumab groups and placebo were not statistically significant . The Committee noted that the majority of efficacy outcomes did not maintain statistical significance compared with placebo when assessed after a 16-week treatment-free follow-up period.

8.10. The Committee noted there were no significant adverse events identified in the three trials. The most commonly reported adverse events were nasopharyngitis and headache. No anaphylactic reactions occurred during the ASTERIA II and GLACIAL studies. Three suspected anaphylaxic type clinical events occurred in ASTERIA I (two during omalizumab treatment and one 142 days post treatment), but were judged not to be true anaphylaxis, not attributed to study drug and dipyrone-induced anaphylaxis respectively.

8.11. The Committee noted omalizumab has been approved for funding for the treatment of severe urticaria by the Scottish Medical Committee (SMC), European Medicines Agency (EMA), National Institute for Health Care and Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH) subject to confidential rebates. The Committee noted that the Pharmaceutical Benefits Advisory Committee (PBAC) is to review an application for funding at its November 2015 meeting.

8.12. The Committee considered that omalizumab would most likely be used after high dose antihistamines and leukotriene inhibitors (currently not funded for urticaria in New Zealand) and would replace ciclosporin. The Committee considered that omalizumab had fewer adverse events than ciclosporin and required reduced haematological surveillance with fewer blood tests and would have less adverse effects than long-term systemic corticosteroid use.

8.13. The Committee considered that if omalizumab were to be listed for this indication, it should be in the HML only and restricted to clinical immunologists and dermatologists. The Committee noted that there can be difficulties with the subcutaneous injection and, that as 150 mg is the only strength currently listed, patients would require two injections for the 300 mg dose. The Committee also noted that restricting prescribing to Dermatologists and Clinical Immunologists may prove to be difficult for patients as access to these two specialities was limited in some parts of the country.

8.14. The Committee considered the restrictions recommended by NICE may be suitable for Special Authority criteria. The Committee noted the NICE guidelines include the cessation of omalizumab after dose 4 if there had been no response, and the cessation at the end of a 6 dose course to ascertain if remission is sustained, with resumption of treatment only if there is relapse. The Committee considered that improvements in the Quality of Life rather than improvements in itchiness scores should be the measure of effectiveness.

8.15. The Committee noted that patients in the placebo arms of the clinical trials also responded well and that it considered the best estimate of treatment effect to be the

difference between placebo and omalizumab as this is a condition that can spontaneously remit.

8.16. The Committee considered that the quality of the evidence was strong, that the effectiveness may be good and that the side effect profile is acceptable. The Committee recommended that the current Special Authority criteria for omalizumab be widened to include the treatment of severe chronic spontaneous urticaria with a low priority. The Committee recommended the application be referred to the Dermatology Subcommittee for the development of specific Special Authority criteria to ensure only those who would benefit most have access to omalizumab.

9. Eplerenone in heart failure patients, with an ejection fraction ≤40% and diabetes or at high risk of diabetes, or intolerant to optimal dosing of spironolactone

Application

9.1. The Committee considered an application from Te Arai BioFarma to fund eplerenone (Inspra) on the Pharmaceutical Schedule for patients with heart failure with an ejection fraction ≤40% and with diabetes or with a high risk of diabetes, and for patients with heart failure who are intolerant to optimal dosing of spironolactone.

Recommendation

9.2. The Committee **recommended** that funding of eplerenone on the Pharmaceutical Schedule for patients with heart failure with an ejection fraction ≤40% and diabetes, or with a high risk of diabetes should be declined.

9.3. The Committee **recommended** that eplerenone be funded on the Pharmaceutical Schedule for patients with heart failure who are intolerant to optimal dosing of spironolactone with a low priority, subject to Special Authority criteria/hospital restrictions.

9.4. The Committee **recommended** that the funding application for eplerenone be reviewed by the Cardiovascular Subcommittee to examine the strength of the evidence and determine appropriate Special Authority criteria/hospital restrictions.

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

Discussion

9.6. The Committee noted that eplerenone is currently registered in New Zealand to reduce the risk of cardiovascular death in combination with standard therapy in patients who have evidence of heart failure and left ventricular impairment within 3 to 14 days of an acute myocardial infarction. The Committee noted that the application was for a currently unregistered indication.

9.7. The Committee noted the main evidence supporting the use of eplerenone in patients with heart failure comes from two randomised control trials, EPHESUS (Pitt et al. Cardiovasc Drugs Ther 2001;15:79-87) and EMPHASIS HF (Zannard et al. Eur J Heart Fail 2010;12:617-22).

9.8. The Committee noted in the EPHESUS RCT, all-cause mortality was reduced when eplerenone was commenced in addition to conventional therapy, within the first 30 days post myocardial infarction, in patients with an LVEF ≤40% and signs of heart failure.

9.9. The Committee considered that the evidence provided in the application was of a high quality, but was of a low strength, as the populations studied within the data are of limited relevance to the population and indication for which funding is sought.

9.10. The Committee considered that there was insufficient evidence to demonstrate that eplerenone was clinically equivalent to spironolactone for the management of chronic heart failure.

9.11. The Committee noted that clearly defined Special Authority criteria/hospital restrictions would be required to direct its use to people with heart failure who are intolerant of optimal doses of spironolactone and recommended this application be reviewed by the Cardiovascular Subcommittee of PTAC.

Heart failure with an ejection fraction ≤40% and diabetes or at high risk of diabetes

9.12. The Committee noted that the application for eplerenone to be used for heart failure with an ejection fraction ≤40% and diabetes or at high risk of diabetes is currently an unlicensed indication unless it is initiated within 3 to 14 days of an acute myocardial infarction.

9.13. The Committee noted that the evidence supporting use in heart failure with an ejection fraction ≤40% and diabetes or at high risk of diabetes came from a small randomised control trial (Yamaji et al. American Heart Journal 2010, 160, 5, 915-921). In the 17 patients within the relevant subpopulation receiving spironolactone there was a small but statistically significant increase in both HbA1c and cortisol levels. These increases were not seen in the 28 patients receiving eplerenone. The Committee considered that although the HbA1c increases were statistically significant, they were of uncertain clinical relevance.

9.14. The Committee also noted an analysis of the EMPHASIS HF study by Preiss et al. (Eur. J. Heart Fail. 2012;14:909-15) was supportive of this suggested indication because it reported that the use of eplerenone had no effect on new-onset diabetes in patients with chronic heart failure in contrast to spironolactone. Spironolactone does appear to effect Hba1c levels although the clinical significance of this was unclear.

9.15. The Committee was uncertain why the supplier identified an ejection fraction cut off of ≤40% in the proposal. Although, the Committee noted that this criterion was amongst the entry criteria for the EPHESUS study, this evidence was in a post myocardial infarction population, and therefore of debatable relevance in determining Special Authority criteria for the proposed funded indications.

Heart failure patients intolerant to optimal dosing of spironolactone

9.16. The Committee noted that the application for eplerenone to be used for patients with heart failure intolerant to optimal dosing of spironolactone is currently an unlicensed indication unless it is initiated within 3 to 14 days of an acute myocardial infarction. The Committee noted that it would be unlikely for spironolactone intolerance to be identified within that 14 day post myocardial infarction time period.

9.17. The Committee noted eplerenone was developed as a more selective aldosterone antagonist than spironolactone, with significantly less progestogen related and anti-androgenic adverse effects. The Committee considered that the two main reasons for discontinuing spironolactone are likely to be related to either anti-androgenic or hyperkalemic effects.

9.18. The Committee noted that in the RALES RCT of spironolactone in patients with NHYA Class 3 and 4 heart failure (Pitt et al. NEJM 1999;341:709-17), 8% of the entire treatment group discontinued spironolactone due to adverse effects, compared with 5% in the placebo group. 73% of the study population was male, and of these 10% in the

spironolactone treatment group developed gynecomastia or breast pain, compared with 1% in the control group. Discontinuation attributed to this event was 2% in the treatment group and 0.2% in the control group.

9.19. The Committee noted that the meta-analysis of randomised control trials by Ezekowitz et al. (Eur Heart J. 2009;30:469-77) found a rate of gynaecomastia of 4.3% in patients treated with spironolactone compared with 0.6% in controls, and that the rate of gynaecomastia in eplerenone trials was 0.5% in both treatment and control groups.

9.20. The Committee noted that in the EPHESUS trial of eplerenone the rates of discontinuation and adverse events were low. The incidences of gynecomastia and impotence in men and breast pain in women were no greater than placebo. Rates of discontinuation for adverse events were approximately equal between treatment and placebo groups at around 4.5%. In contrast, withdrawal due to adverse event in EMPHASIS HF was relatively high at 13.8% in the eplerenone treatment group and 16.2% in the placebo group. Low numbers withdrew due to hyperkalaemia or breast disorders and there is no detail given as to the cause of other withdrawals.

9.21. The Committee considered that quality of life gains may be achieved from reduced anti-androgenic adverse reactions. The Committee considered it could not be confident of the likely proportion of patients in whom these effects would lead to discontinuation of spironolactone therapy, but considered that that the majority of patients developing gynaecomastia do not discontinue therapy.

9.22. The Committee noted the applicant's figure for people developing adverse drug reactions on spironolactone to be 10%. The Committee considered that the number of patients discontinuing spironolactone therapy due to an intolerable adverse drug reaction would be closer to 2%.

9.23. The Committee noted that availability of a funded alternative to spironolactone may influence what patients consider unacceptable side effects and that well defined Special Authority criteria would be required to ensure access only to those patients who would benefit most from the use of eplerenone.

Risk of hyperkalaemia

9.24. The committee noted from the respective datasheets that the definitions of renal impairment constituting a contraindication for spironolactone and eplerenone were different. Spironolactone is contraindicated in 'significant impairment of renal function' whereas eplerenone is contraindicated in patients with a creatinine clearance <50ml/min.

9.25. The Committee noted that in all the studies presented, patients were excluded from participation if they had serum potassium level >5 mmol/L. The Committee noted that rates of serious hyperkalaemia in the RALES study were relatively low at 1% in the placebo group and 2% in the spironolactone group. In EPHESUS, the incidence of serious hyperkalaemia (>6 mmol/L) was 5.5% in the treatment group and 3.9% for placebo. In EMPHASIS HF, hyperkalaemia (>5.5 mml/L) occurred in 11.8% of eplerenone patients and 7.2% of the placebo group, with serious hyperkalaemia occurring in 2.5% and 1.9% respectively (these patients had eGFR >30 ml/min). Treatment with eplerenone reduced the incidence of hypokalaemia compared with placebo.

9.26. The Committee considered that there was insufficient evidence that the use of eplerenone in patients with renal impairment or at risk of hyperkalaemia was more or less likely to cause hyperkalemia compared with spironolactone.

10. Aflibercept for diabetic macular oedema

Application

10.1. The Committee reviewed an application from Bayer NZ Limited for the listing of aflibercept on the Hospital Medicines List (HML) for the treatment of diabetic macular oedema (DMO).

Recommendation

10.2. The Committee **recommended** that the application for listing of aflibercept as a first line anti-vascular endothelial growth factor (anti-VEGF) treatment for diabetic macular oedema be declined.

10.3. The Committee deferred making a recommendation regarding the funding of aflibercept as a second line anti-VEGF treatment for DMO at this time. The Committee recommended the application be referred to the Ophthalmology Subcommittee for consideration as second line anti-VEGF treatment for DMO at their next meeting. The Committee also requested input from the Subcommittee regarding an estimation of the number of patients that would require second line treatment.

10.4. 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; (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

10.5. The Committee noted the incidence and prevalence of DMO was likely to increase in the future as the number of patients with type 2 diabetes increases. Members noted that DMO represents a significant source of morbidity in patients with diabetes type 1 and 2, and can lead to blindness. Members also noted that there is a higher incidence and burden of illness of DMO in Maori and Pacific peoples.

10.6. The Committee noted the currently funded treatments for DMO are laser therapy and intravitreal bevacizumab, which is listed on the HML for ocular neovascularisation or exudative ocular angiopathy. Members noted that laser therapy is effective at preserving vision but less effective at restoring lost vision. Members also noted that the use of bevacizumab in DMO is similar to that in wet age-related macular degeneration (wAMD), as it is an off-label indication and also uses the "treat and extend" protocol, where the effect of one intravitreal injection of bevacizumab 1.25 mg can last up to 8 weeks.

10.7. The Committee noted its previous recommendation of running a competitive process for a second line anti-VEGF treatment of wAMD following bevacizumab treatment. Members considered the relevance of this recommendation to DMO and noted the evidence was different in this setting and required further consideration.

10.8. The Committee noted a systemic review by Ford et al. (BMJ Open 2013 Mar 1;3(3)) assessing the evidence for anti-VEGF agents and steroids in DMO. Members noted that this study was conducted before publication of the VIVID and VISTA studies. Members also noted that the review reported that intravitreal ranibizumab and bevacizumab are effective in DMO but that there was insufficient evidence available at the time of the review to make any conclusions for aflibercept.

10.9. The Committee noted a Cochrane Review (Virgili, Gianni, et al. Cochrane Database Syst Rev 2015;10:CD007419) which consisted of 18 studies assessing the efficacy and safety of anti-VEGF treatments in DMO. All patients had central DMO and moderate vision loss. Anti-VEGF treatments reviewed were ranibizumab, bevacizumab, pegatanib, and aflibercept. Primary outcome measure of vision improvement was a 'gain or loss of 3+ lines of visual acuity at 1 year' (ETDRS). Members noted when compared with laser therapy, anti-VEGF (ranibizumab, bevacizumab and aflibercept) were superior with a RR 3.60 (2.70-4.80) more likely to gain 3+ lines at 1 year. All anti-VEGF treatments were

also superior to sham injections, and subgroup analysis showed no difference between bevacizumab, ranibizumab and aflibercept in reaching primary outcome. Members noted safety data was reassuring but high risk patients (past cardiovascular event and poorly controlled hypertension) were excluded so questioned if the safety results were applicable for many diabetic patients.

10.10. The Committee noted the Cochrane review provided good evidence suggesting that bevacizumab and ranibizumab in DMO was superior to laser, and there is no additional benefit when laser or steroid was added to treatment. Members also noted there was good evidence in the literature and in clinical practice indicating intravitreal bevacizumab is safe, and that earlier theoretical safety concerns of it being a larger molecule could cause damage the eye had not eventuated.

10.11. The Committee noted that there was good evidence for the use of ranibizumab in DMO. Members noted that the RESOLVE (Massin et al. Diabetes Care. 2010;33:2399–405) and , RISE studies (Nguyen et al. Ophtha 2012;119:789-801) showed 0.3 mg dose was superior to 0.5 mg, and the RIDE study (Nguyen et al. Ophtha 2012;119:789-801) showed the inverse was true. The READ-3 study (Do et al. Eye (Lond). 2015 Jul 31. doi: 10.1038/eye.2015.142) results showed no difference between the 2 mg and 0.5 mg dosing at 6 months. Members noted that the correct dose of ranibizumab was likely between 0.3 mg to 0.5 mg.

10.12. The Committee considered three studies for aflibercept – Do et al. Ophtha 2011;118:1819-26, Korobelnik et al. Ophtha 2014;121:2247-54, and Wells et al. N Engl J Med 2015;372:1193-203:

- The DA VINCI study (n=219) conducted by Do et al. (Ophtha 2011;118:1819-26) was a phase II clinical trial to determine optimal dosing of aflibercept in patients with DMO compared with laser therapy. A total of 5 regimens were evaluated: 0.5 mg every 4 weeks; 2 mg every 4 weeks; 2 mg 3 initial monthly doses and then every 8 weeks (“treat and extend” protocol); 2 mg for 3 initial monthly doses and then on an as-needed (PRN) basis and laser therapy. Members noted that at 6 months, all treatments were superior to laser therapy and there were no clinically significant differences between the aflibercept groups. Members also noted that the “treat and extend” protocol used in study was consistent with current clinical practice.

- The paper by Korobelink et al. 2014 (Ophtha 2014;121:2247-54) reported on the VISTA (n=466) and VIVID (n=406) studies. These were phase III double masked randomised controlled trials conducted over one year. Treatment groups were 2 mg every 4 weeks (2q4), 2 mg every 8 weeks (2q8) (after five monthly injections) and laser therapy with sham injections. The primary outcome assessed showed both the 2q4 and 2q8 groups in both VISTA and VIVID trials had significantly greater best-corrected Visual Acuity (BCVA) letter improvements from baseline when compared with the laser control group (+12.5+/-9.5 letters and +10.7+/-8.2 letters versus +0.2+/-12.5 letters ($P < 0.0001$) in VISTA, respectively; and +10.5 +/- 9.5 letters and +10.7 +/- 9.3 letters versus +1.2 +/- 10.6 letters ($P < 0.0001$) in VIVID, respectively). Secondary outcomes, showed significantly more eyes treated with in the aflibercept group gained ≥ 15 letters from baseline at week 52, and mean reductions in central retinal thickness (CRT) was greater in the aflibercept group when compared with the laser control group. Adverse effects reported were similar between all groups. Members noted participants in the VIVID trial had significantly higher mean CRT than those in the patients in the laser and 2Q8 groups in the VISTA study. Members noted that mean HbA1C of patients in both studies was lower than that of typical patients seen in clinical practice. Members considered most patients that need anti-VEGF treatment would have end stage retinopathy with a higher HbA1C and their response to aflibercept may differ compared with patients in the trial.

- A randomised direct head to head comparison study by Wells et al. 2015 (N Engl J Med 2015;372:1193-203) compared bevacizumab, ranibizumab, and aflibercept (n=660). Primary outcome measure of mean change in visual acuity from baseline to 1 and 2 years. Results showed a greater mean improvement in the visual-acuity (VA) letter score at one year with aflibercept than with bevacizumab and ranibizumab (13.3 vs. 9.7 and 11.2, respectively; P<0.001 for aflibercept vs. bevacizumab and P = 0.03 for aflibercept vs. ranibizumab). Members noted although aflibercept showed a greater mean improvement of VA, this did not equate to clinical superiority as this effect was dependent on baseline visual acuity. Members considered sub-analysis of patients showed aflibercept had a greater mean improvement in VA in patients with poorer baseline visual acuity (<20/50) than bevacizumab and ranibizumab (18.9 ± 11.5 vs 11.8 ± 12 and 14.2 ± 10.6 respectively). Members noted central subfield thickness also decreased at one year follow-up by 169±138 µm with aflibercept, 101±121 µm with bevacizumab, and 147±134 µm with ranibizumab. Adverse events reported were similar across all three groups however post hoc analysis revealed a higher frequency of cardiac and vascular events in the ranibizumab group.

10.13. The Committee noted aflibercept 2 mg had a similar therapeutic effect in DMO when compared to the currently listed alternative bevacizumab 1.25 mg. Members also noted PBAC's November 2014 finding, that the aflibercept 2 mg was clinically equivalent to ranibizumab 0.5 mg; and bevacizumab 1.25 mg in effectiveness. Members also considered aflibercept 2 mg injection to be non-inferior to bevacizumab 1.25 mg and ranibizumab 0.5 mg in terms of effectiveness and safety.

10.14. The Committee noted aflibercept's mechanism of action was slightly different to that of ranibizumab and bevacizumab, and that theoretically aflibercept has broader specificity, as it is a VEGF-Trap which binds to VEGF-A, VEGF-B and placental growth factor (PIGF). However, members questioned whether the pharmacological difference resulted in different clinical outcomes.

10.15. The Committee noted that bevacizumab is the only listed agent on the HML that can be used for DMO and considered there is an unmet need for patients who do not respond or are intolerant to bevacizumab. Members considered there to be an unmet health need with accessing secondary care services for some patients, and that blindness due to DMO was avoidable. However, the committee noted it would need to evaluate the evidence for a second line anti-VEGF agent in DMO before considering giving a recommendation.

10.16. The Committee noted it was reasonable to use NICE recommendations on aflibercept to help form the restriction criteria. Members considered the restriction criteria for patient eligibility should include baseline CRT ≥ 400 µm and a visual acuity measure.

10.17. The Committee considered there was insufficient evidence to suggest the use of aflibercept would result in reduced changes in health sector expenditure through longer intervals between treatments.

11. Clostridium botulinum Type A toxin funding options

Application

11.1. The Committee considered a paper from PHARMAC staff seeking clinical advice on potential future funding options for Clostridium botulinum type A toxin in DHB hospitals.

Recommendation

11.2. The Committee considered that the all Clostridium botulinum type A toxin products currently registered in New Zealand could be used for the same or similar clinical uses with comparable safety and efficacy, and **recommended** that PHARMAC proceed with a competitive process for Clostridium botulinum type A toxin supply to DHB hospitals.

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 Clostridium botulinum type A toxin, produced by *Clostridium botulinum*, is a potent natural poison that blocks normal synaptic release of acetylcholine from the neuromuscular junction. This blockade causes non-permanent muscle relaxation, which can be useful in the treatment of disorders characterised by excessive muscle tone.

11.5. The Committee noted that two brands of Clostridium botulinum type A toxin are listed on the Hospital Medicines List (HML; Part II of Section H of the Pharmaceutical Schedule) for use in DHB hospitals without restrictions: inj 100 u vial (Botox) and inj 500 u vial (Dysport). The Committee noted that a third brand (Xeomin) was registered with Medsafe in New Zealand but was not listed on the HML.

11.6. The Committee reviewed DHB hospital usage data and DHB clinician feedback collated by PHARMAC staff, and noted that there appears to be significant regional variation in utilisation for the various indications, which is likely due to regional variation in access to the relevant specialist services. The Committee also noted regional variation in the comparative usage of the two brands currently listed on the HML. The Committee noted that some DHBs may have negotiated their own pricing arrangements directly with a supplier, resulting in higher/exclusive use of a particular brand.

11.7. The Committee noted the DHB hospital expenditure on Clostridium botulinum type A toxin was currently approximately $4 million per year and appeared to be increasing. The Committee noted that given the relatively high hospital expenditure on Clostridium botulinum type A toxin and the existence of competition, PHARMAC staff had sought advice from the Committee on potential future funding options in this market. More specifically, one of the options currently being investigated by PHARMAC staff is whether a competitive process seeking price proposals for a particular brand to have sole unrestricted listing in the HML, effectively creating a mandated first-line or sole-supply brand for some or all indications, could be clinically appropriate.

11.8. The Committee noted that the therapeutic injection of Clostridium botulinum type A toxin is performed in many clinical settings, for a large number of uses (many of which are not approved indications) and by an expanding population of clinicians. The Committee considered that the majority of the increasing usage in DHB hospitals may be for neurological indications.

11.9. The Committee noted that Clostridium botulinum type A toxin is an established treatment for patients with certain movement disorders, including blepharospasm and limb dystonias. It is also a potential treatment option for spasticity in the setting of traumatic brain injury, cerebral palsy, and post-cerebrovascular accident, hyperactivity of the detrusor muscle of the bladder, conditions characterised by hypersecretion (such as hyperhidrosis and sialorrhea), the prevention of chronic migraine and a variety of gastrointestinal conditions including achalasia and chronic anal fissure.

11.10. The Committee noted that each Clostridium botulinum type A toxin preparation contains botulinum neurotoxin, comprised of a heavy amino acid chain (100kD) and a light chain (50kd). Preparations of onabotulinumtoxinA (Botox) contain the toxin complexed with naturally occurring non-toxic proteins, producing a molecular weight of approximately 450kD. Two botulinum neurotoxin molecules form a dimer with a molecular weight of approximately 900kD. The biochemical composition of abobotulinumtoxinA (Dysport) is not known but contains a mixture of L complex (600kD and M complex 300kD). For the

incobotulinumtoxinA (Xeomin) preparation, the complexing proteins are removed, yielding a molecular weight of 150kD. IncobotulinumtoxinA contains only active neurotoxin, whereas onabotulinumtoxinA is likely to contain denatured/inactive neurotoxin. Upon injection, complexing proteins, if present, rapidly disassociate from the toxin (Drugs R D. 2010;10:67-73).

11.11. The Committee noted that one unit of Clostridium botulinum type A toxin corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice, performed in a mouse potency assay The Committee considered determining interchangeability of different brands based on intraperitoneal lethal dose (LD50) in mice was not possible as the relevant LD50 methods are not available for comparison. These methods are retained in-house by each of the product manufacturers, most likely for commercial reasons.

11.12. The Committee reviewed a large number of published placebo-controlled trials in a range of indications provided by the supplier of abobotulinumtoxinA which the Committee considered provided reasonable evidence of the efficacy and safety of abobotulinumtoxinA.

11.13. The Committee noted a double-blind, randomised, dose-ranging study by Wohlfarth et al. (J Neurol. 2008;255:1932–9) comparing the relative potency of onabotulinumtoxinA (Botox) to abobotulinumtoxinA. This study investigated the dose equivalence, diffusion characteristics (spread) and safety of in 79 volunteers. Both formulations caused significant and similar reductions in compound muscle action potential amplitude in the target muscle (extensor digitorum brevis, EDB) 2 weeks after injection, with effects persisting to 12 weeks. The authors concluded a dose-equivalence ratio of less than 3:1 is likely. This conclusion on relative potency was supported by Gollomp (Pract. Neurol. 2011;9:27-33).

11.14. The Committee noted a study by Kollewe et al. (J Neural Transm. 2015;122:427-31) examining the treatment, efficacy and adverse effect data on blepharospasm patients treated with either onabotulinumtoxinA, abobotulinumtoxinA or incobotulinumtoxinA for at least eight consecutive treatments. Two hundred and eighty-eight patients (208 females, 80 males, age 62 ± 12 years) were included in this study. The treatment time was 11.2 ± 4.1 years covering 10,701 injection series. Doses were 47 ± 10 MU for onabotulinumtoxinA, 120 ± 35 MU for abobotulinumtoxinA, and 62 ± 11 MU incobotulinumtoxinA. 85 % of all patients had stable doses. The onset of the therapeutic effect was after 6.1 ± 3.3 days and its duration lasted 10.2 ± 3.5 weeks. Adverse effect frequency was not significantly different between the products.

11.15. The Committee noted a study by Oliveira de Morais et al. (J Drugs Dermatol. 2012;11:216-9) comparing the efficacy of four Clostridium botulinum type A toxin in the treatment of hyperdynamic forehead lines. The Committee noted that one of the formulations used in this trail is not currently registered for use in New Zealand. A different treatment was applied to the each side of the forehead of the 12 male participants and visually compared monthly until 150 days post treatment. OnabotulinumtoxinA and incobotulinumtoxinA were used at a 1:1 dose ratio, while abobotulinumtoxinA was used at a 3:1 dose ratio compared with the other treatments. All patients responded, with no statistically significant differences in effectiveness between the treatments.

11.16. The Committee noted data presented by Frevert and Dressler (Biologics, 2010;4:325-32) comparing onabotulinumtoxinA and incobotulinumtoxinA efficacy using compound muscle action potential M-wave amplitudes following repeated injections into the extensor digitorum brevis muscle of each foot. The Committee noted there were no statistically significant differences between the two treatments in terms of degree of paralysis, onset of action, or duration of paralysis (although time to onset of action was slightly earlier with incobotulinumtoxinA). Neither treatment had any effect on adjacent muscles.

11.17. The Committee noted a study by Dressler (Eur J Neurol. 2009;16:2-5) examining the therapeutic outcome and adverse effects of switching patients to incobotulinumtoxinA who were previously treated with onabotulinumtoxinA. Two hundred and sixty-three patients (91 with dystonia, 84 with spasticity, 17 with hemifacial spasm and re-innervation synkinesias, 64 with hyperhidrosis and 7 with hypersalivation) were converted in a blinded fashion to incobotulinumtoxinA using a 1:1 conversion ratio and identical treatment parameters. Therapeutic outcome and adverse effects were monitored by neurological examination and structuralised interviews. In 223 patients (all except those with axillary hyperhidrosis) incobotulinumtoxinA was used continuously throughout a 3 year period. Patients with dystonia received 261.5 ± 141.0 MU, patients with spasticity 450.5 ± 177.1 MU, patients with hemifacial spasm and reinnervation synkinesias 44.7 ± 19.5 MU, and patients with hyperhidrosis 286.9 ± 141.6 MU. There were no subjective or objective differences between treatments with respect to onset latency, maximum efficacy, duration of therapeutic effect, and adverse effect profiles. Long-term use did not reveal additional safety relevant aspects.

11.18. The Committee noted a small retrospective chart review by Boileau (Toxicon. 2013;68:107) comparing the onset and duration of effect, doses, time between visits and safety profiles in 11 adult cervical dystonia patients first treated with multiple onabotulinumtoxinA treatment cycles who then switched to an equal amount of incobotulinumtoxinA. No significant differences were observed in each of the parameters (dose, onset of effect, duration of effect and days between patient visits) when comparing treatment cycles. Safety was comparable between the treatments.

11.19. The Committee noted a study by Grosset et al. (J Rehabil Med. 2015;47:183-6) exploring the dose equivalence ratio and treatment costs for abobotulinumtoxinA and incobotulinumtoxinA for patients with focal dystonias by patient chart review. Patients were switched from abobotulinumtoxinA to incobotulinumtoxinA with a mean dose ratio of 4.07 (standard deviation (SD) 0.50). After switching, incobotulinumtoxinA dose requirements remained stable; the mean (SD) dose ratio at the end of the review period (52–219 weeks after switching) was 3.89 (SD 0.58). Injection intervals also remained stable after switching.

11.20. The Committee considered that the available evidence supported the view of Gollomp (Pract. Neurol. 2011;9:27-33) who concluded that the clinical consequences of differences in molecular weight, protein content, and diffusion between preparations are likely negligible and suggests there is no reason to believe that the preparations of Clostridium botulinum type A toxin cannot all be used for the same indications.

11.21. The Committee considered that, based on the available evidence, a reasonable estimate of dose equivalence would be 1:2.5 for onabotulinumtoxinA compared with abobotulinumtoxinA; and 1:1.2 for onabotulinumtoxinA compared with incobotulinumtoxinA. However, the Committee noted that there are variations in the trials and the dose equivalence ratios may depend on the indication being treated.

11.22. The Committee considered that the presence or absence of complexing proteins does not appear to influence diffusion, due to the fact that the native toxin rapidly dissociates from the complexing proteins upon injection.

11.23. The Committee noted that having smaller vial sizes available to match the smaller doses often used may help to reduce wastage and cost. Small doses are common in number of indications including ophthalmology, sialorrhea and paediatrics. The Committee considered that in most instances where small quantities are used, vials would most likely not be used for multiple patients, and instead the remainder of the dilution would be disposed of at the completion of the procedure.

11.24. The Committee considered that, based on the available evidence, a competitive process that could result in only one listed brand of Clostridium botulinum type A toxin would be clinically reasonable, noting the potential for significant savings in this market.

11.25. The Committee considered that if a competitive process was progressed, and a brand that is currently not listed in Section H of the Pharmaceutical Schedule was to be listed as a result of that process, the evidence for that product should be evaluated by the Committee prior to that listing occurring.

11.26. The Committee considered that prior to running a competitive process it would be worthwhile seeking further information from clinicians on what implementation may be required if there was a move to restrict the available listed brands, including from neurologists and urologists who appear to be the specialists using the largest quantities of Clostridium botulinum type A toxin.

12. Aripiprazole depot injection (Abilify Maintena) for schizophrenia

Application

12.1. The Committee considered an application from Lundbeck Australia Pty Ltd for the funding of aripiprazole depot injection (Abilify Maintena) for the treatment of schizophrenia.

Recommendation

12.2. The Committee **recommended** that aripiprazole depot injection (Abilify Maintena) should be funded subject to the following Special Authority criteria (and similar hospital restrictions) only if it was cost-neutral to paliperidone depot injection:

> **Initial application** from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
> Either:
> 1 The patient has had an initial Special Authority approval for risperidone depot injection, paliperidone depot injection or olanzapine depot injection; or
> 2 All of the following:
> 2.1 The patient has schizophrenia; and
> 2.2 Has tried but failed to comply with treatment using oral atypical antipsychotic agents; and
> 2.3 Has been admitted to hospital or treated in respite care, or intensive outpatient or home-based treatment for 30 days or more in last 12 months.
>
> **Renewal** from any relevant practitioner. Approvals valid for 12 months where the initiation of aripiprazole depot injection has been associated with fewer days of intensive intervention than was the case during a corresponding period of time prior to the initiation of an atypical antipsychotic depot injection.

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

Discussion

12.4. The Committee noted that schizophrenia is a common, severe, disabling condition. The prevalence in New Zealand of approximately 0.5% in the overall population and higher, approximately 1%, in Māori.

12.5. The Committee noted that there is a large range of funded oral and injectable antipsychotics, including aripiprazole tablets, which are funded subject to Special Authority restrictions for patients with schizophrenia or related psychoses, who have tried risperidone or quetiapine, and as a last-line treatment for autism spectrum disorder in patients aged under 18 years (an off-label indication). The Committee considered that there were no particular problems with access to, or availability of, current treatments for schizophrenia. However, the Committee noted that there is a lack of available

treatments that are effective in improving the significant psychosocial morbidity associated with cognitive effects in patients with schizophrenia.

12.6. The Committee noted that there is a generally held view that depot antipsychotics improve compliance compared with oral presentations; however, there appears to be little evidence in support of this view. Members noted that, just as it is not uncommon for patients to forget or refuse to take oral antipsychotics, patients also may refuse or forget to take depot injections.

12.7. The Committee noted that aripiprazole depot injection (Abilify Maintena) is registered in New Zealand for the maintenance of clinical improvement in the treatment of schizophrenia. It is supplied as single-dose (300 mg or 400 mg), lyophilised powder for reconstitution with water for injections. The recommended starting and maintenance dose of aripiprazole depot is 400 mg given as a deep intramuscular gluteal injection once monthly (no more frequently than one injection every 26 days).

12.8. The Committee noted that the supplier (Lundbeck Australia Pty Ltd) was seeking funding of aripiprazole depot injection subject to the same or similar criteria that currently apply to the three funded atypical antipsychotic depot injections (olanzapine, risperidone and paliperidone). The Committee noted that the supplier had selected paliperidone depot injection as the treatment comparator for its funding submission, which the Committee considered was reasonable given that paliperidone depot injection had recently become the most widely used depot injection in New Zealand.

12.9. The Committee noted that the supplier had provided three key lines of evidence to support its application, discussed below: direct comparison between aripiprazole tablets and aripiprazole depot injection; direct comparison between aripiprazole depot injection and paliperidone depot injection; and an indirect comparison between aripiprazole depot injection and paliperidone depot injection. The Committee noted that all the studies were industry funded by the developer of aripiprazole depot injection, Otsuka.

12.10. Trial 31-07-247 (ASPIRE EU; Fleischhacker et al. Br J Psychiatry 2014;205:135-44) was a 38-week, double-blind, active-controlled, non-inferiority study in which 662 responders to oral aripiprazole were randomised 2:2:1 to aripiprazole once-monthly 400 mg, oral aripiprazole (10–30 mg/day) or aripiprazole once-monthly 50 mg (a dose below the therapeutic threshold for assay sensitivity). The primary outcome was the Kaplan–Meier estimated impending relapse rate from the date of randomisation to the end of week 26. At week 26, Kaplan–Meier estimated impending relapse rates were 7.12% for aripiprazole once-monthly 400 mg and 7.76% for oral aripiprazole; this difference (70.64%, 95% CI 75.26 to 3.99) excluded the predefined non-inferiority margin of 11.5%. The most common adverse events associated with aripiprazole 400 mg injection were insomnia, akathisia, headache and weight decrease/increase, which were reported by 9–12% of patients. The authors considered that the safety profile of aripiprazole once-monthly was comparable with oral aripiprazole and consistent with that reported for oral aripiprazole in previous registrational maintenance studies and was also consistent with data from another maintenance study of aripiprazole once-monthly 400 mg versus placebo (Kane et al. J Clin Psych 2012;73:617-24). The Committee noted that only two-thirds of patients completed the trial and that the trial did not include quality of life measures. The Committee considered that the trial provided good quality and strength evidence that aripiprazole depot injection was as effective as oral aripiprazole.

12.11. Trial 14724A (QUALIFY) was a 28-week, randomised, open-label rater-blinded, study comparing aripiprazole depot injection with paliperidone depot injection every 4 weeks in 295 patients with schizophrenia changing from oral antipsychotics. The primary endpoint assessed non-inferiority and subsequently superiority on change from baseline to week 28 in Quality of Life Scale (QLS) total score analysed using a mixed model for repeated measurements. A total of 100/148 (67.6%) of aripiprazole and 83/147 (56.5%) of paliperidone patients completed 28 weeks of treatment. In treated patients, adverse events were the most frequent reason for discontinuation (11.1% of aripiprazole

patients, 19.7% of paliperidone patients). The difference in change from baseline to week 28 on QLS total score was statistically significant (4.67 [95%CI: 0.32;9.02], p=0.036), which is concluded by the supplier to confirm non-inferiority and establish superiority of aripiprazole compared with paliperidone. The Committee considered that this finding supported non inferiority but not superiority. The respective changes were 7.47±1.53 for aripiprazole and 2.80±1.62 for paliperidone. Adverse events occurring at rates ≥5% in either group in the treatment continuation phase were weight increased (aripiprazole 10.1%; paliperidone 15.6%), psychotic disorder (aripiprazole 2.5%; paliperidone 5.5%) and insomnia (aripiprazole 2.5%; paliperidone 5.5%). The Committee considered that there were a number of limitations with the study, including that it was not published, was not double-blinded, no intention-to-treat analysis was reported clearly, a mixed effect model repeat measurement was used to analyse the endpoint which increases the chance of a Type I error, information was not provided regarding the location of the study, and the supplier noted a high likelihood of bias. The Committee noted that QLS was an unusual outcome measure and that trials of antipsychotics traditionally use relapse rates as their primary outcome measure. However, the Committee considered that this was a reasonable scale, well designed with good validity and reliability coefficients.

12.12. The indirect comparison of aripiprazole depot injection and paliperidone depot injection was based on two placebo-controlled trials: a double-blind, randomised controlled trial comparing aripiprazole depot injection with placebo in patients with schizophrenia who were stabilised on aripiprazole depot injection (ASPIRE US, Kane et al. J Clin Psychiatry 2012;73:617-24) and a double-blind, randomised controlled trial comparing paliperidone depot injection with placebo in patients with schizophrenia who were stabilised on paliperidone depot injection (Hough et al. Schizophrenia Res 2010;116:107-17). The supplier's analysis demonstrated no statistically significant difference between the two treatments on the primary efficacy outcome. The Committee noted that the trial designs were similar and the primary outcome measures (time to first relapse) were the same; however, the patient groups differed in terms of the illness duration and it appeared that the patients in the aripiprazole study were less unwell.

12.13. The Committee noted an additional study provided in the supplier's submission: trial 31-08-003 (Ishigooka et al. Schizophrenia Res. 2015;161:421-28), which was a 52-week double-blind study in patients stabilised on oral aripiprazole, designed to verify non-inferiority of aripiprazole depot injection to oral aripiprazole in Asian patients with schizophrenia. The primary endpoint was Kaplan–Meier estimated rate of non-exacerbation of psychotic symptoms/non-relapse at week 26. At week 26, the primary endpoint was achieved by 95.0% of patients in the aripiprazole depot injection group and 94.7% of patients in the oral aripiprazole group. The between-group difference of 0.3% (95% CI: −3.9,4.5), demonstrating a non-inferiority margin of −3.9% which is above the pre-defined non-inferiority limit (−15%). Discontinuation rates due to all reasons were 25.9% in the aripiprazole depot injection group and 33.5% in the oral aripiprazole group. The authors reported that aripiprazole depot injection was as tolerated as well as oral aripiprazole. The Committee noted that the study was conducted to support the Asian regulatory dossier and considered that it was not generalisable to the New Zealand setting due to the different ethnic mix of the population. The Committee did not consider this study further.

12.14. The Committee noted another publication of a trial that the supplier had excluded from its submission because it was an acute trial: this was a 12-week, randomised, double-blind, placebo-controlled trial in which adults experiencing an acute psychotic episode were given aripiprazole depot injection (400 mg once monthly, n=168) or placebo (n=172) (Kane et al. J Clin Psychiatry 2014;75:1254-60). A least squares mean change from baseline to endpoint (week 10) favoured aripiprazole on the primary efficacy measure of Positive and Negative Syndrome Scale (PANSS) total score (treatment difference, –15.1 [95% CI, –19.4 to –10.8]; p<0.0001). Common adverse events seen with aripiprazole versus placebo were increased weight (16.8% vs 7.0%), headache (14.4% vs 16.3%) and akathisia (11.4% vs 3.5%).

12.15. Overall, the Committee considered that the supplier had presented reasonable quality evidence to support non-inferiority of aripiprazole depot injection to oral aripiprazole and to paliperidone depot injection. The Committee noted that none of the effect sizes (where reported) were large and most of the trials had selected patients likely to respond to aripiprazole depot injection during the pre-randomisation phase, which was different from the 'real world' setting. The Committee considered that insufficient evidence had been presented to support the superiority of aripiprazole depot injection to oral aripiprazole or paliperidone depot injection.

12.16. The Committee considered that, on the basis of the available evidence, aripiprazole depot injection would likely provide similar therapeutic effect to oral aripiprazole and any of the funded atypical antipsychotic depot injections (risperidone, paliperidone, olanzapine). The Committee considered that the main benefit from funding aripiprazole depot injection would be to provide increased treatment choice for clinicians and patients.

12.17. The Committee considered that the supplier's suggestion that costs associated with managing adverse effects are likely to be lower with aripiprazole depot injection due to a comparatively favourable metabolic effect profile were speculative. The Committee noted that while the supplier promotes aripiprazole as causing less weight gain than some of the other atypical antipsychotics, weight gain is still experienced by a significant proportion of patients on aripiprazole. However, the Committee considered that aripiprazole may be useful in patient groups particularly at risk of metabolic issues for example Māori and Pacific Island peoples.

12.18. The Committee considered that aripiprazole depot injection would be unlikely to create any significant changes in healthcare expenditure other than direct treatment costs. The Committee noted that if patients switched from olanzapine depot injection to aripiprazole depot injection there would be less post-injection monitoring time; however, members noted that the way olanzapine depot injection monitoring was currently managed it did not require additional staff resource.

12.19. The Committee considered that the patient group most likely to benefit from aripiprazole depot injection was those in whom oral aripiprazole is effective but adherence to oral treatment is problematic.

12.20. The Committee considered that aripiprazole depot injection would likely be taken in combination with a number of potential other treatments (eg oral antipsychotics, benzodiazepines, anticonvulsants) but this would be no different from treatments co-prescribed with the currently funded antipsychotic depot injections.

12.21. The Committee considered that if aripiprazole depot injection was funded, many patients on oral aripiprazole may move to depot treatment and there was a significant likelihood of patients switching to aripiprazole depot injection from another depot, for example if they were hospitalised on another depot. The Committee considered that funding aripiprazole depot injection would likely grow the antipsychotic depot injection market to at least the same extent that paliperidone depot injection did.

12.22. The Committee considered that there appeared to be no evidence to support a price premium of aripiprazole depot injection over paliperidone depot injection. The Committee noted that even if aripiprazole depot injection was priced the same as paliperidone depot injection this would likely result in a significant cost to the Combined Pharmaceutical Budget, due to an overall increase in the use of antipsychotic depot injections versus the status quo.

12.23. The Committee noted the finding of the 2006 Te Rau Hinengaro: The New Zealand Mental Health Survey (http://www.health.govt.nz/publication/te-rau-hinengaro-new-zealand-mental-health-survey)that a significant number of Māori patients with mental

health disorders do not receive the treatment they need. However, the Committee considered that funding aripiprazole depot injection would be unlikely to impact on this.

13. Methylphenidate for treatment-resistant depression

Application

13.1. The Committee considered an application from a clinician for the funding of methylphenidate on the Pharmaceutical Schedule for treatment-resistant depression.

Recommendation

13.2. The Committee **recommended** that the application for methylphenidate in treatment-resistant depression be declined.

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

Discussion

13.4. The Committee noted that methylphenidate immediate-release 5, 10 and 20 mg tablets and sustained-release 20 mg tablets are currently funded subject to Special Authority and hospital restrictions for patients with attention deficit and hyperactivity disorder (ADHD) and narcolepsy, and methylphenidate extended-release 18 mg, 27 mg, 36 mg and 54 mg tablets and modified-release 10 mg, 20 mg, 30 mg and 40 mg capsules are currently funded subject to Special Authority and hospital restrictions as a second-line treatment for ADHD.

13.5. The Committee noted that PHARMAC had received funding applications from clinicians for widening access to methylphenidate (all currently funded presentations) for use in treatment-resistant depression, depression in terminally ill patients, and apathy in patients with traumatic brain injury, all of which are off-label indications.

13.6. The Committee noted that methylphenidate is only registered for use in New Zealand for the treatment of attention deficit and hyperactivity disorder (ADHD) and narcolepsy. The Committee noted that under regulation 22 of the Misuse of Drugs Regulations 1977, methylphenidate can only be prescribed by a psychiatrist or paediatrician (for ADHD only), an internal medicine specialist (for narcolepsy only) or a palliative care specialist (for use in palliative care only), or by any other medical practitioner on the written recommendation of one of these specialists (only for the relevant condition as specified for each specialty).

13.7. The Committee noted that the Mental Health Subcommittee had reviewed the funding of methylphenidate in treatment-resistant depression, palliative care and traumatic brain injury in July 2013.

- The Subcommittee recommended that the application for methylphenidate in palliative care be declined, given the potential risks and poor evidence of clinical benefit; this recommendation was accepted by PTAC at its November 2013 meeting. The Committee noted that PHARMAC staff had sought the Committee's advice as to whether this decline recommendation remains appropriate.

- The Subcommittee deferred making a recommendation for traumatic brain injury pending PHARMAC staff seeking expert advice and advice from the Neurological Subcommittee and PTAC. The Committee noted that expert advice had been sought and this was due to be considered by the Neurological Subcommittee in November 2015. The Committee deferred discussion of methylphenidate in

traumatic brain injury pending the outcome of the Neurological Subcommittee's review.

- The Subcommittee also deferred making a recommendation for treatment-resistant depression pending publication of the new Royal Australian New Zealand College of Psychiatrists (RANZCP) guidelines for the treatment of depression. The Committee noted that a draft of the new guidelines had recently been consulted on and PHARMAC staff had sought the Committee's advice on this indication.

Treatment-resistant depression

13.8. The Committee noted that depression is a common condition with 10% of patients in primary care presenting with depressive symptoms. The lifetime risk of depression is 15% and the 12-month prevalence is 4.1%. Approximately 54% and 70% of patients recover within 6 months and 12 months, respectively, with approximately 12%-15% developing unremitting chronic illness. The Committee noted that rates of diagnosed mood disorders in Maori adults is higher than non-Maori and is increasing. The Committee noted that Māori have a marginally higher 12-month prevalence of major depressive disorder compared with other ethnic groups and Māori are 1.6 times more likely to have experienced high levels of psychological distress (indicating a high probability of a depressive disorder) than non-Māori.

13.9. The Committee noted that treatment-resistant depression was not currently a legally permitted indication for methylphenidate under the Misuse of Drugs Regulations, although it is possible for individual prescribers to apply for Ministerial Approval for this use for a named patient. The Committee noted that any recommendation to fund methylphenidate for treatment-resistant depression would not be progressed by PHARMAC for funding unless treatment-resistant depression was added to the list of permitted indications under the Misuse of Drugs Regulations.

13.10. The Committee noted that the applicants had provided no published evidence in support of the use of methylphenidate for treatment-resistant depression, but that PHARMAC staff had provided several publications identified from a literature search.

13.11. The Committee noted the findings of a meta-analysis and two systematic reviews, which were not supportive of the use of methylphenidate in depression.

- Candy et al. Cochrane Database Syst Rev 2008;16:CD006722. This was a meta-analysis of randomised controlled trials evaluating psychostimulants (including methylphenidate) in the treatment of adults with depression. The primary outcome was depression symptoms. The authors noted that the overall quality of trials was low, with low sample sizes, high risk of selection bias, detection and performance bias, attrition bias and publication bias. The main positive finding reported was from three small trials (62 participants) showing that oral psychostimulants, as monotherapy, significantly reduced short-term (<4wk) depressive symptoms in comparison with placebo (Standardised Mean Difference -0.87, 95% CI -1.40, -0.33) with non-significant heterogeneity. However, the Committee noted that only one of these trials studied methylphenidate and members considered that the clinical significance of this finding is unclear. A separate analysis of three trials (130 participants) comparing rates of clinical response found no difference between intervention and control (OR 1.01, CI 0.48-2.09). In the short term, psychostimulants were acceptable and well tolerated, but in the medium term (5-12wk) side effects were much more frequently reported by patients taking psychostimulants (OR 7.22 95% CI 2.21-23.57) (two trials with 90 participants). No trials examined the longer term effect of psychostimulants. Tolerance and dependence were under-evaluated.

- Zhou et al. J Clin Psychiatry 2015;76:e487-98. This was a systematic review and meta-analysis of 48 randomised trials with 6,654 participants comparing

augmentation agents (including methylphenidate) with each other and with placebo in treatment-resistant depression. There were two methylphenidate trials included in the analysis (Patkar et al. J Clin Psychopharmacol 2006;26:653–6 and Ravindran et al. J Clin Psychiatry 2008;69:87-94). In contrast to quetiapine, aripiprazole, thyroid hormone and lithium, methylphenidate was no more effective than placebo on the primary efficacy measure (the proportion of patients who responded to treatment), OR 1.42 (95% CI 0.81-2.5) or the secondary efficacy measure (remission rates). There was no difference between methylphenidate and placebo in acceptability or tolerability.

- Fleurence et al. Psychopharmacol Bull 2009;42:57-90. This was a review of augmentation strategies for patients with major depressive disorder who do not benefit from first-line treatment with antidepressants. The authors identified the same two methylphenidate trials analysed by Zhou et al 2015, above, and found that there was no evidence of clinical efficacy of augmentation with methylphenidate.

13.12. The Committee noted the reports of two randomised controlled trials which did not support the efficacy of methylphenidate in treatment-resistant depression:

- Ravindran et al. J Clin Psychiatry 2008;69:87-94. This was a multicenter, double-blind, randomised, placebo-controlled, parallel-group, 5-week trial in 145 patients with major depressive disorder and who had not responded to 1 to 3 previous antidepressant monotherapies (including current antidepressant) of adequate dose and duration. Augmentation therapy was initiated with methylphenidate 18 mg extended-release tablets, increased to a maximum dose of 54 mg, in addition to the current antidepressant. Efficacy scales included the Montgomery-Asberg Depression Rating Scale (MADRS; the primary endpoint), 7 atypical items from the 31-item HRSD, the Clinical Global Impressions-Severity of Illness (CGI-S) scale, the CGI-Improvement scale (CGI-I), the Sex Effects scale, the Multidimensional Assessment of Fatigue (MAF) scale, and the Apathy Evaluation Scale (AES). There was no statistically significant difference between the groups at endpoint on the MADRS. Methylphenidate was superior to placebo in improving apathy at endpoint as measured by the AES. The Committee noted that this effect would be expected as a normal physiological response to a psychostimulant and queried its clinical significance given that patients did not have severe apathy symptoms at baseline. The authors stated that the MAF scores demonstrated statistical significance favouring the active group at all visits except endpoint; however, the MAF scores were not provided in the paper and p values were reported without confidence intervals. No differences were observed on other secondary measures, including the CGI-I and CGI-S. There were no clinically significant findings on electrocardiogram. Methylphenidate was well tolerated with minimal side effects, which included headache (22% of patients), nausea (11%) and reduced appetite (6%). The Committee noted that Rizvi et al. (J Clin Psychopharmacol 2014;34:755-9) in a letter to the editor, report the findings of a secondary analysis of data from this trial. They found that early changes in apathy and fatigue predicted response to adjunctive methylphenidate and proposed that assessing these symptoms may be more relevant in determining treatment benefit than changes in global depression scores.

- Patkar et al. J Clin Psychopharmacol 2006;26:653–6. This was a four-week, randomised, double-blind, placebo-controlled trial of augmentation of antidepressants with methylphenidate extended-release tablets (18-54 mg extended-release tablets per day) in sixty patients with treatment-resistant depression. The primary efficacy measure was change in the 21-item HDRS from randomisation to end of treatment. Secondary efficacy measures were change in CGI-I and CGI-S scores and Beck Depression Inventory. There were no statistically significant differences between the methylphenidate (n = 30) and placebo (n = 30)

groups in reduction in 21-item HDRS scores (methylphenidate group, –6.9; placebo group, –4.7) from baseline to end of treatment (F1,47=1.24, P=0.22). There were no significant differences between methylphenidate and placebo on the secondary efficacy measures. Methylphenidate appeared well tolerated with no major safety signals identified.

13.13. The Committee noted two studies from the same authors in older adults with depression:

- Lavretsky et al. Am J Psychiatry 2015;172:561-9. This was a 16-week randomised double-blind placebo-controlled trial in 143 older outpatients diagnosed with major depression (41% of whom had treatment-resistant depression) comparing treatment response in three groups: methylphenidate plus placebo (n=48); citalopram plus placebo (n=48); and methylphenidate plus citalopram (n=47). The primary outcome was defined as the change in depression severity. Remission was defined as HDRS-24 score of 6 or below. Secondary outcomes included measures of anxiety, apathy, quality of life, and cognition. Citalopram daily doses ranged between 20–60 mg (mean 32 mg. which the Committee noted was higher than currently recommended doses in New Zealand); methylphenidate daily doses ranged between 5–40 mg (mean 16 mg). The formulation of methylphenidate was not specified, other than to state that patients took capsules containing 2.5 mg methylphenidate. The dropout rate was high in all groups. All groups showed significant improvement in the severity of depression. The improvement in depression severity and CGI score was more prominent in the methylphenidate and citalopram group compared with methylphenidate and placebo and citalopram and placebo (P<0.05). The rate of improvement in the methylphenidate and citalopram group was significantly faster than that in the citalopram and placebo in the first four weeks of the trial. The difference in remission rates between citalopram plus placebo and citalopram plus methylphenidate was not statistically significant. The groups did not differ on cognitive improvement or the number of side-effects.

- Lavretsky et al. Am J Geriatr Psychiatry 2006;14:181-5. This was a 10-week, double-blind randomised controlled trial in 16 older adults with major depression (13 of whom had treatment-resistant depression) were randomised to receive either citalopram 20-40 mg daily plus placebo (n=6) or citalopram 20-40 mg daily plus methylphenidate 2.5 mg twice daily (formulation not specified) titrated to 10 mg daily dose by the end of week one (n=10). Four patients in the citalopram plus methylphenidate group discontinued before the end of the study, three of whom withdrew because of side effects. An accelerated response was observed by week 3 in five patients receiving citalopram plus methylphenidate and in no patients receiving citalopram plus methylphenidate.

13.14. The Committee also noted the findings of an open-label study in patients with bipolar depression which did not find a significant benefit of methylphenidate as an add-on therapy (El-Mallakh et al. Bipolar Disord. 2000;2:56-9) and an uncontrolled open-label case series in patients with bipolar (n=27) or unipolar (n=23) depression given methylphenidate or dexamphetamine as add-on or monotherapy where 34% of patients reported a distinct improvement in their depression (Parker and Brotchie. Acta Psychiatr Scand 2010:121: 308–14).

13.15. The Committee noted that international guidelines either do not recommend the use of methylphenidate in treatment-resistant depression (National Institute for Health and Care Excellence; NICE) or include it in a list of potential augmentation agents that could be considered (American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder –grade III recommendation “may be recommended on the basis of individual circumstances”; British Association for Psychopharmacology – recommendation strength level C). The Committee noted that the draft update of the RANZCP Clinical Practice Guideline for Mood Disorders, as

issued for public consultation in June 2015 (https://www.ranzcp.org/Files/Publications/RANZCP-CPG-Mood-Disorders-public-consultation-draf.aspx), do not recommend stimulants for treatment-resistant depression, stating "At present there is insufficient evidence to recommend the routine use of psychostimulants as an augmentation strategy." However, the draft guidelines do recommend the use of stimulants as a last-line treatment augmentation option for bipolar disorder depression treatment, based on the findings of the Parker and Brotchie (Acta Psychiatr Scand 2010;121:308-314) publication described above.

13.16. The Committee considered that, overall, the studies were of low quality and the strength of the evidence was mostly weak. The Committee considered that the available evidence did not support the efficacy of methylphenidate in producing clinically meaningful improvements in depression scores. The Committee considered that there was insufficient evidence to support a health benefit of methylphenidate in treatment-resistant depression.

13.17. The Committee noted that there are a large number of alternative pharmacological strategies for managing treatment-resistant depression, for example quetiapine, aripiprazole, thyroid hormone and lithium as identified in the Zhou et al. 2015 systematic review mentioned above, and strategies summarised in the RANZCP draft guidelines. The Committee considered that there were no particular problems with access to alternative treatments.

13.18. The Committee noted that methylphenidate formulations and doses have differed between the small randomised controlled trials and case series in the literature. The immediate release tablets have been used in doses ranging from 10-30 mg daily and the extended release formulation has been used in doses of up to 54 mg per day.

13.19. The Committee considered that methylphenidate was associated with a risk of diversion and illicit use in the treatment-resistant depression setting, as well as in the palliative care setting discussed below.

13.20. Overall, the Committee considered that methylphenidate should not be funded for treatment-resistant depression, primarily on the basis of poor evidence of effectiveness and availability of alternative treatment options.

Terminal illness

13.21. The Committee noted that the causality of fatigue in terminal illness is complex and multidimensional, and is likely to be affected by disease and the illness experience, depression/anxiety, grief, and medications, particularly opiates, benzodiazepines and low dose antipsychotics (for management of nausea) commonly used in palliative medicine. Members noted that targeting the symptom of fatigue with a psychostimulant may not be analogous to targeting nausea with an antiemetic nor pain with an analgesic. The Committee noted the difficulties in conducting robust clinical trials in this group of patients who are heterogeneous, may not wish to participate in clinical trials & have short life expectancy.

13.22. The Committee noted that there is a large number of available antidepressants that can be used to manage depression in terminally ill patients, although the three to six week time to onset of action can be problematic in patients with a short life expectancy.

13.23. The Committee noted a number of publications relating to the use of methylphenidate for the treatment of fatigue in terminal illness, most of which showed no evidence of benefit from methylphenidate on fatigue:

- Mucke et al. Cochrane Database Syst Rev. 2015;5:CD006788.
- Bruera et al. J Clin Oncol 2006;24:2073-8.
- Butler et al. Int J Radiat Oncol Biol Phys 2007;69:1496-501.
- Escalante et al. Cancer J 2014;20:8-14.

- Moraska et al. J Clin Oncol 2010;28:3673-9.
- Roth et al. Cancer 2010;116:5102-10.

13.24. The Committee noted a number of publications relating to the use of methylphenidate for the treatment of depression in terminal illness, which had mixed results:

- Ng et al. 2014;24:491-8.
- Centeno et al. BMJ Support Palliat Care 2012;2:328-33.
- Homsi et al. Am J Hosp Palliat Care 2001;18:403-7.
- Kerr et al. J Pain Symptom Manage 2012;43:68-77.
- Macleod AD. J Pain Symptom Manage 1998;16:193-8.

13.25. The Committee considered that the studies were generally low strength and quality and there were significant limitations in the studies with positive findings (Homsi et al. 2001, Kerr et al. 2012 and Macleod et al. 1998) in terms of study size, methodology and analysis.

13.26. The Committee noted that methylphenidate was generally well tolerated although it was commonly associated with the types of side effects that would be expected following administration of a stimulant, including restlessness and palpitations.

13.27. The Committee reconfirmed its previous endorsement of the recommendation from the Mental Health Subcommittee to decline the funding of methylphenidate for use in palliative care, on the basis of poor evidence of efficacy.

14. Tocilizumab (Actemra) for rheumatoid arthritis (amending access)

Application

14.1. The Committee considered an application from a clinician, with support from the New Zealand Rheumatology Association (NZRA), to widen access to tocilizumab (Actemra) to remove the requirement to trial rituximab prior to tocilizumab in patients with rheumatoid arthritis seronegative for both rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies.

Recommendation

14.2. The Committee **recommended** that the hospital restrictions for tocilizumab should be amended to remove the requirement to trial rituximab in patients with rheumatoid arthritis seronegative for both anti-cyclic citrullinated peptide [CCP] antibodies and rheumatoid factor (RF) only if this would be cost-neutral to the status quo hospital expenditure on rituximab and tocilizumab for this patient group.

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

Discussion

14.4. The Committee noted that tocilizumab (Actemra) is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass which binds to human interleukin 6 (IL-6) receptors. Tocilizumab is currently listed on the Hospital Medicines List (HML), funded for last-line biologic treatment of rheumatoid arthritis; first-line biologic treatment of rheumatoid arthritis in patients who cannot take methotrexate; first-line biologic treatment of systemic juvenile idiopathic arthritis; and first- or second-line biologic treatment of adult-onset Still's disease.

14.5. The Committee noted that the application requested removal of the requirement to trial rituximab prior to tocilizumab in patients with rheumatoid arthritis where patients were

seronegative for both anti-cyclic citrullinated peptide [CCP] antibodies and rheumatoid factor (RF), on the basis that rituximab is less likely to be effective in seronegative patients. The Committee noted the Rheumatology Subcommittee had recently (October 2015) reviewed the application.

14.6. The Committee noted the following supporting information provided in the application:

- A randomised controlled trial of rituximab plus methotrexate versus methotrexate alone that reports a stratified analysis by RF status (the REFLEX study; Cohen et al. Arthritis Rheum 2006;9:2793-806). The subgroup analysis by RF status found that the proportion who are RF positive with an American College of Rheumatology (ACR)20 response were rituximab 54% versus placebo 19%, odds ratio (OR) 5.0, and in RF negative patients 41% had an ACR20 response with rituximab versus 12% with placebo, OR 5.1; with a P value for the interaction of 0.90 (i.e. there is no statistically significant interaction). This paper reports no evidence that the response to rituximab depends on RF antibody status although the point estimates suggest that those who are RF negative do worse on average.

- An abstract (Isaacs et al. Ann Rheum Dis 2009;68(Suppl3):442) and associated poster that the Committee considered was superseded by a subsequently published meta-analysis from the same authors provided by PHARMAC staff and discussed below.

- A poster from Tak and colleagues (Poster 833 at American College of Rheumatology 2006) which is a more detailed report of the lack of differential effect of rituximab versus placebo when anti-CCP is added into the analysis for the Cohen study described above.

- Pooled data from 10 European registries showing that rituximab was most effective in patients with rheumatoid arthritis who were autoantibody positive and in those for whom no more than one previous tumour necrosis factor (TNF)-alpha inhibitor has failed (Chatzidionysiou K et al. Ann Rheum Dis 2011;70:1575-80). The Committee noted that this paper reports a prospective cohort study based on registry data from hospitals using rituximab for rheumatoid arthritis and reporting six month outcomes. For Disease Activity Score based on 28 joint counts (DAS28) the mean improvement from baseline was 1.9 for RF+ versus 1.6 for RF- but no actual numbers or CI for the difference by group were presented. The point estimate for the difference was 0.3 and it is reported to be statistically significant. There did not appear to be a multi-variate adjusted analysis of DAS response. For European League Against Rheumatism (EULAR) moderate or better response the difference after six months was 66.2% versus 57.9%, an OR of 1.4 and although the analysis results are not shown is reported as not statistically significant after adjustment for a number of other predictors of response. The authors highlight that anti-CCP positive predicted response better than RF status and that those who were antibody negative in fact also responded to rituximab. The Committee noted that the paper is a registry based cohort study so a number of other factors (clinician knowledge of antibody status, differences in other prognostic factors) and unmasked assessment of outcomes could explain the associations. Furthermore, the association with RF status was weak or not detectable, although possibly stronger for anti-CCP status.

- A retrospective cohort study of patients who were given infliximab or tocilizumab presented in abstract form only (Sato et al. Arthritis Rheum 2013;65(Suppl 10):S1010-1). No actual numbers or associations are presented for the tocilizumab group. There were major differences between the treatment groups, for example methotrexate and past biologic use was far higher in the infliximab cohort. The Committee considered that this abstract did not contain information relevant to the application.

- A narrative review (Jones and Ding. Clin Med Insights Arthritis Musculoskelet Disord 2010;3:81-9). The Committee noted that the lead author is the lead author of the 'AMBITION' randomised controlled trial of tocilizumab monotherapy versus methotrexate in rheumatoid arthritis (Jones et al. Ann Rheum Dis 2010;69:88-96), and the review article presents a subgroup analysis of AMBITION by RF status that didn't appear to be included in the main trial publication. The analysis shows no evidence of a difference in response to tocilizumab compared with methotrexate by RF status, although RF-negative patients appeared to respond less well to both treatments.

14.7. The Committee noted the additional information provided by PHARMAC staff:

- An individual patient data meta-analysis of four industry sponsored randomised controlled trials of rituximab by antibody status with a post-hoc division of participants by RF and/or anti-CCP status (Isaacs et al. Ann Rheum Dis 2013;72:329–36). The Committee noted that the authors chose not to do an interaction analysis by antibody status and estimated the difference between antibody positive and negative within treatments, which means that they have not addressed the question of whether RF status influences treatment response. The main analysis was DAS-28 where one study (REFLEX) had the largest difference between RF/anti-CCP positive and negative in the rituximab arm of about 1 unit compared with the other three studies of 0.25 units, pooled difference 0.35 (0.12 to 0.58 units). The authors do not present the ACR20 results because 'the effects were in the same direction but with large uncertainty'.

- A systematic review of cohort studies which report responses to treatment with abatacept, rituximab and tocilizumab by RF status (Maneiro et al. Semin Arthritis Rheum 2013;43:9-17). For ACR20 actual numbers aren't provided but in RF positive patients rituximab had OR for treatment effect of 1.95 (1.24 to 3.08) based on three studies (54% vs 41%, 63% vs 40%, 85% vs 75%) and tocilizumab had OR of 1.51 (1.21 to 1.90) based on three studies (70% vs 56%, 73% vs 67%, 61% vs 52%). The Committee considered that, although not comparative, this is consistent with both rituximab and tocilizumab having a higher relative effect in antibody positive patients than antibody negative patients but is also consistent with antibody negative patients just doing less well with these two therapies.

14.8. Overall, the Committee considered that the strength of the evidence is weak and the quality is moderate. The Committee noted that there are no randomised trials comparing tocilizumab to rituximab in rheumatoid arthritis and there are no randomised controlled trials that have prospectively stratified by antibody status for either tocilizumab or rituximab.

14.9. The Committee considered that no compelling evidence had been provided to support an effect of antibody status on response to rituximab. For the purposes of PHARMAC's analyses, the Committee considered that the response rate to rituximab reported in the REFLEX study (ACR20 of 51%, as advised by PTAC in May 2008) should be used, noting that this rate applies to both seropositive and seronegative patients.

14.10. Similarly, the Committee considered that there is no evidence that the effect of tocilizumab differs by antibody status. For the purposes of PHARMAC's analyses, the Committee considered that an ACR20 response rate for tocilizumab of 43% should be used (response rate advised by PTAC in November 2011 for patients in whom previous TNF-alpha inhibitors have been ineffective), and this rate applies to both seropositive and seronegative patients.

14.11. The Committee reiterated its previous view that there is no evidence that strongly supports the use of either rituximab or tocilizumab first following TNF-alpha inhibitor failure, and there is no evidence regarding the use of tocilizumab post rituximab or vice

versa. However, the Committee considered that additional lines of biologic treatments are likely to be associated with diminishing efficacy returns.

14.12. The Committee considered it likely that if the criteria were amended and patients tried tocilizumab first after TNF-alpha inhibitor failure, patients in whom tocilizumab did not work would likely then try rituximab. The Committee noted the view of the Rheumatobgy Subcommittee that this should be permitted, and the Committee noted that this was similar to the current situation where patients tried rituximab first and then tocilizumab if rituximab was unsuccessful.

14.13. The Committee considered that no evidence had been provided to suggest that health outcomes would differ by sequencing tocilizumab ahead of rituximab compared with sequencing rituximab ahead of tocilizumab in seronegative patients; particularly as there is very weak evidence of a difference in response by antibody status as a possible way of choosing how to do the sequence.

14.14. The Committee considered that if the tocilizumab restrictions were amended as requested, approximately 10 additional new patients per year would access tocilizumab rather than rituximab first after TNF-alpha inhibitor failure.

14.15. The Committee considered that sequencing tocilizumab ahead of rituximab in this patient population would be unlikely to create any significant changes in health-sector expenditure other than for direct treatment costs (including the cost of infusion).

14.16. The Committee considered that there were no clinical reasons not to make the requested changes to the tocilizumab restrictions; however, given the lack of evidence of clinical benefit provided, the Committee considered that the main consideration would be fiscal. In this regard, the Committee considered that any changes should not be associated with any increased cost to the hospital pharmaceutical budget.