

# **Record of the Pharmacology and Therapeutic Advisory Committee (PTAC) Meeting Held on 8 & 9 February 2018**

Minutes of PTAC and Subcommittees of PTAC are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

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

PTAC and Subcommittees of 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

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data

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

### **Present:**

#### **PTAC members:**

Mark Weatherall (Chair)  
Alan Fraser  
Giles Newton-Howes  
Jane Thomas  
Jennifer Martin  
Marius Rademaker  
Matthew Strother  
Melissa Copland  
Sean Hanna  
Simon Wynn Thomas  
Stuart Dalziel  
Stephen Munn  
Tim Stokes

## **1. Subcommittee Minutes**

### **Immunisation Subcommittee**

- 1.1. The Committee noted and accepted the record of the Immunisation Subcommittee of PTAC held on 26 July 2017.
- 1.2. The Committee noted and accepted the record of an Immunisation Subcommittee of PTAC email discussion completed on 26 January 2018, regarding urgent Subcommittee advice and a recommendation that access to maternal pertussis vaccination be widened to include women in their second trimester of pregnancy with a high priority.

### **Anti-Infective Subcommittee**

- 1.3. The Committee noted the partial record of the Anti-Infective Subcommittee meeting held on 2 November 2017, covering the Subcommittee's discussion on pre-exposure prophylaxis for prevention of HIV (PrEP).
- 1.4. The Committee noted that PHARMAC had already made and notified a decision to fund PrEP. The Committee noted that PHARMAC may seek clinical advice from any source, including directly from the Subcommittee. However, members also noted that Subcommittee minutes are not official PTAC advice until they have been reviewed and accepted by PTAC.
- 1.5. Members discussed the key evidence for the Subcommittee's decision. Members considered the populations groups of the trial may differ from the New Zealand population at risk. Members considered the evidence indicated a relatively high number needed to treat to avoid one instance of HIV infection.
- 1.6. Members considered that restricting initial applicants to named prescribers or on the recommendation of one would be a barrier to access. Members were unclear if the recommendation to restrict initial applicants meant that prescribers of antiretroviral treatment would also be reviewing people seeking prophylaxis.
- 1.7. Members noted PHARMAC's intent to review the criteria for PrEP about 12 months after listing. The Committee considered this should include reporting on rates of infection in the funded population group.

### **Cardiovascular Subcommittee**

- 1.8. The Committee noted the complete record of the Cardiovascular Subcommittee meeting held on 27 September 2017.

- 1.9. The Committee noted paragraph 3.6, in which the Subcommittee recommended that rosuvastatin be funded as a third-line cholesterol lowering agent with a high priority. The Committee noted that PTAC had previously recommended this with a medium priority, and that the subcommittee minutes did not discuss new trial evidence to support a change in priority. The Committee did not accept the Subcommittee's new priority and instead reiterated its previous recommendation that rosuvastatin be funded as a third-line cholesterol lowering agent after treatment failure with, or intolerance to, both simvastatin and atorvastatin, with a medium priority.
- 1.10. The Committee noted paragraph 3.8, in which the Subcommittee recommended PTAC review its low priority recommendation for eplerenone and in which the Subcommittee considered patients with gynaecomastia are a distinct group. The Committee considered that no new trial evidence was discussed by the Subcommittee, although noted the opinion of the Subcommittee that patients with gynaecomastia have a high health need. However, in the absence of new evidence regarding this need, and the extent to which this would be met by eplerenone, the Committee reiterated its previous recommendation that eplerenone should be funded for patients with heart failure and an ejection fraction of less than 40% who are intolerant to optimal dosing of spironolactone, with no restriction on the reason for intolerance, with a low priority.
- 1.11. The Committee noted paragraph 5.7, in which the Subcommittee recommended that another novel oral anticoagulant agent (NOAC) be funded for those unable to take dabigatran, especially those with poor renal function, with a high priority. The Committee accepted the recommendation. The Committee, however, considered that the availability of reversal agents does affect clinicians' choices of anticoagulation.
- 1.12. The Committee noted paragraph 5.13, in which the Subcommittee reviewed IV aspirin for use during interventional neuro-radiology procedures when intracranial stent or coils are being used, and recommended that IV aspirin be funded with a high priority. The Committee considered that rectal aspirin also has rapid absorption and could potentially be useful. The Committee noted that slippage is possible in the use of IV aspirin to other clinical situations. The Committee accepted the recommendation of the Subcommittee but also recommended that the funded indication be closely limited.
- 1.13. The Committee noted paragraph 11.2, in which the Subcommittee recommended that aspirin, atorvastatin, and ramipril combination pills be funded with a medium priority. The Committee noted it had considered this application in August 2016 and had stated that applications for fixed-dose combination pills should only be considered if they provided evidence regarding clinical outcomes rather than surrogate outcome measures. The Committee considered that the evidence reviewed by the Subcommittee did not meet this standard. The Committee did not accept the recommendation of the Subcommittee. The Committee reiterated its opinion that such applications should only be considered if they provided evidence of benefit of actual clinical outcomes. In this context the Committee recommended that the application for aspirin, atorvastatin, and ramipril combination pills be declined.
- 1.14. The Committee noted that the Subcommittee gave a high priority to the combination sacubitril and valsartan. The Committee noted that there was an ongoing clinical trial comparing valsartan against the combination of sacubitril and valsartan, and that this trial would clarify whether the mortality benefit, and other possible clinical benefits, would be realised. However, the Committee accepted the Subcommittee's recommendation.
- 1.15. The Committee accepted the remainder of the minutes of the September 2017 Cardiovascular Subcommittee meeting.

### **Respiratory Subcommittee**

- 1.16. The Committee noted the complete record of the Respiratory Subcommittee meeting held on 4 August 2017.

- 1.17. The Committee noted that a draft version of this minute had previously been brought to the Committee in November 2017, when it commented on those minutes, rather than accepting them before ratification by the Subcommittee.
- 1.18. The Committee noted that the wording of the Subcommittee's recommendation in paragraph 6.8 (which related to changing the age restriction for access to dornase alfa for the treatment of cystic fibrosis) differed from the draft version which was reviewed by the Committee in November 2017. The Committee noted that the Subcommittee recommended that the age restrictions be changed from the under 5 years age and 5 & over criteria to under 7 years age and 5 & over criteria. The Committee considered that this change more accurately reflects the intent of giving children more time to learn how to properly conduct spirometry testing and for their lungs to adequately mature. The Committee considered that this proposal should be progressed with a high priority.
- 1.19. The Committee noted that paragraph 6.21 (which related to widening access to omalizumab for the treatment of severe asthma), paragraphs 7.39 and 7.40 (which proposed additional criteria for pirfenidone and for nintedanib (should it be listed)), and paragraph 9.15 (which proposed to widen access to pirfenidone) had previously been noted by the Committee at the November 2017 PTAC meeting.
- 1.20. The Committee noted the Subcommittee's recommendation in paragraph 10.19 for mepolizumab for the treatment of severe allergic eosinophilic asthma. The Committee recommended that, given the high cost of this medicine and potential fiscal risks, that this application and the accompanying evidence be brought to PTAC for review.
- 1.21. The Committee noted and accepted the remainder of the minutes of the August 2017 Respiratory Subcommittee meeting.

#### **Ophthalmology Subcommittee**

- 1.22. The Committee noted the complete record of the Ophthalmology Subcommittee meeting held on 20 September 2017.
- 1.23. The Committee noted paragraph 5.16 which related to chloramphenicol eye ointment being made available on a PSO. The Committee noted that chloramphenicol eye ointment may be used for a wide range of indications ranging from ocular to topical use, and recommended that views from the Anti-Infective Subcommittee be sought around the appropriateness and risks of antimicrobial resistance from having an antibiotic ointment available on PSO.
- 1.24. The Committee noted paragraph 5.19 which related to compounded antibiotic eye drops being used in hospitals. The Committee considered that it should be the responsibility of hospital chief pharmacists to request and share formulations of compounded products used by their DHB hospitals with other DHB hospitals.
- 1.25. The Committee noted that paragraphs 7.1 to 7.26 relating to anti-VEGF agents for ophthalmic use had previously been discussed and noted at the November 2017 PTAC meeting.
- 1.26. The Committee noted and accepted the remainder of the minutes of the September 2017 Ophthalmology Subcommittee meeting.

#### **Rheumatology Subcommittee**

- 1.27. The Committee noted the complete record of the Rheumatology Subcommittee meeting held on 17 October 2017.
- 1.28. The Committee noted that the Subcommittee had been presented with the results of an audit of adalimumab Special Authorities. The Committee asked to see these results as well.
- 1.29. The Committee noted paragraphs 6.2 and 6.3, in which the Subcommittee made recommendations about funding of tofacitinib for rheumatoid arthritis. The Committee noted the recommendations of the Subcommittee. The Committee considered that tofacitinib was a new agent with many potential clinical uses and subsequent high

fiscal risk. The Committee requested that the tofacitinib application be brought to PTAC for review.

- 1.30. The Committee noted and accepted the remainder of the minutes of the October 2017 Rheumatology Subcommittee meeting.

### **Dermatology Subcommittee**

- 1.31. The Committee noted and accepted the minutes of the Dermatology Subcommittee of PTAC meeting held on 20 October 2017. For completeness, where PTAC had additional comments, these are noted below.
- 1.32. The Committee noted that the Dermatology Subcommittee recommended the PASI entry score in the Special Authority initial application criteria for the funded biologics used in severe chronic plaque psoriasis be lowered from “greater than 15” to “greater than 10”; and a DLQI reduction of five or more be added to the Special Authority renewal criteria, in addition to the current PASI 75 reduction, as an alternative assessment of treatment response. The Committee noted that the Subcommittee made these recommendations based on international guidelines rather than published trial data. The Committee considered that the likely number of additional patients being eligible for biologic treatment would be small with low fiscal risk.
- 1.33. The Committee noted that the Dermatology Subcommittee recommended pimecrolimus 1% ointment be listed, either for all patients with atopic dermatitis and without a Special Authority only if cost-neutral to hydrocortisone acetate 1% cream, or only for atopic dermatitis on eyelids and subject to Special Authority criteria, and a maximum of 15 gm per 6 months. The Committee considered that there was a risk of indication creep leading to larger amounts of this product being used.
- 1.34. The Committee noted that the Dermatology Subcommittee recommended tacrolimus ointment (0.03% and 0.1%) be listed for facial atopic dermatitis and subject to Special Authority criteria. The Committee noted that this was given a high priority by the Subcommittee. The Committee considered that there was a potential risk of high volume use of this product due to patient numbers and amount applied topically, with a subsequent high fiscal risk. For this reason, this application could be reviewed by the Committee if further advice was requested by PHARMAC. The Committee otherwise supported the recommendation and proposed Special Authority criteria.

### **Cancer Treatments Subcommittee**

- 1.35. The Committee noted and accepted the record of the Cancer Treatments Subcommittee of PTAC held on 25 August 2018, with the exception of item 11.
- 1.36. In regards to item 11, nivolumab for the second-line treatment of relapsed clear cell renal cell carcinoma, the Committee requested the application be reviewed by PTAC at a future meeting.

## **2. Insulin Glargine for the treatment of type 1 and 2 Diabetes**

### **Application**

- 2.1. The Committee reviewed the application from Sanofi-Aventis for long-acting insulin glargine (Toujeo) for the treatment of type 1 and 2 diabetes mellitus.

### **Recommendation**

- 2.2. The Committee **recommended** that long-acting insulin glargine (Toujeo) for the treatment of type 1 and 2 diabetes be listed only if cost neutral to the health sector.
- 2.3. The Committee **recommended** that PHARMAC staff seek input from the Diabetes Subcommittee on wording for restrictions that would target long-acting insulin glargine (Toujeo) to high need groups, if cost-neutrality could not be achieved.
- 2.4. The Committee took into account, where applicable, PHARMAC’s relevant decision-making framework when considering this agenda item.

## Discussion

- 2.5. The Committee noted that the health need of patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) has been well-documented in PTAC and subcommittee minutes of previous submission of other antidiabetic agents.
- 2.6. The Committee considered that T2DM places a significant burden on patients and the New Zealand Health system, particularly Pacific people, Māori and South Asian populations; which have higher prevalence, more severe, and generally earlier onset of disease. The Committee considered that there were fewer population and/or ethnic differences in the rates T1DM.
- 2.7. The Committee noted that that the causes of T1DM and T2DM are different, and that whilst patients with T1DM start using insulin from the outset to control blood glucose levels, patients with T2DM usually start insulin at a much later stage in disease when oral hypoglycemic agents fail to adequately control the blood sugar levels.
- 2.8. The Committee noted that there are currently a range of short-acting and long-acting insulins listed in the Pharmaceutical Schedule without restrictions. The Committee noted that Toujeo is a more concentrated and a longer acting formulation of insulin glargine than the current subsidized product, Lantus. The Committee noted that Toujeo contained 300 international units (IU) of insulin glargine per mL, whereas the currently listed insulin glargine, Lantus, contained 100 IU per mL. The Committee noted that as Toujeo was more concentrated, less volume is needed to administer the same number of IU as Lantus.
- 2.9. The Committee noted the supplier's submission in its entirety and the following pivotal trials and the relevant extension trials:
  - EDITION 1, Riddle et al. Diabetes Care 2014;37:2725-62
  - EDITION 2, Yki-Jarvinen et al. Diabetes Care 2014;37:3235-43
  - EDITION 3, Bolli et al. Diabetes Obes Metab. 2015;17:386-94
  - EDITION 4, Home et al. Diabetes Care 2015;38:2217-25
- 2.10. The Committee noted that EDITION 1 – 3 were conducted in patients who had T2DM and that EDITION 4 was conducted in patients with T1DM. The Committee noted that the above trials showed that long-acting insulin glargine, Toujeo, was therapeutically equivalent (non-inferior) to insulin glargine, Lantus.
- 2.11. The Committee noted that in terms of risks of severe and/or confirmed nocturnal hypoglycaemia, the above trials showed small statistically significant reductions in the risk of hypoglycaemia with Toujeo compared to Lantus in EDITION 1 and 2 and a non-statistically significant reduction in EDITION 3. The Committee noted that the rates of hypoglycaemia between Toujeo and Lantus were similar in EDITION 4.
- 2.12. The Committee noted that across all trials, a higher dose of Toujeo in terms of IU was needed to achieve a similar level of glucose control as Lantus. The Committee noted that a Toujeo dose 10-18% higher than Lantus may be needed. The Committee considered that clinicians would need to be particularly careful when initiating patients onto Toujeo as the dose would need to be titrated more slowly than with Lantus, due to the long period of time it takes for Toujeo to reach steady state in the body. The Committee considered that there would likely be additional healthcare costs due to increased GP or nurse time when starting or switching patients onto Toujeo.
- 2.13. The Committee considered that overall, Toujeo was well tolerated and that rates of adverse events; such as weight gain, rates of withdrawal, injection site reactions; and serious adverse events, were similar across the different insulin glargine formulations.
- 2.14. The Committee considered that the above trials were of high quality and that the strength of evidence was good.
- 2.15. The Committee recommended that long-acting insulin glargine be listed only if cost-neutral to the health budget as it considered that the clinical benefits of Toujeo were, for most people with T1DM and T2DM, largely the same as that achieved with Lantus.

The Committee noted that higher doses of Toujeo are needed to achieve similar levels of glucose control as that achieved with Lantus, and that the reductions in the risks of hypoglycaemia were small and uncertain, and that additional monitoring was likely to be necessary.

- 2.16. The Committee noted that whilst the benefits of Toujeo and Lantus were largely similar, there may be groups of patients for whom Toujeo would be a more suitable treatment option than Lantus. The Committee considered that Toujeo may be particularly suitable for those patients who are obese or have significant insulin resistance and who are currently injecting large volumes of Lantus. The Committee considered that if cost neutrality between Toujeo and Lantus could not be achieved, that its use should be targeted to patient groups who may derive significant benefits from its listing. The Committee recommended that PHARMAC staff seek input from the Diabetes Subcommittee on wording for restrictions that would target long-acting insulin glargine (Toujeo) to high need groups.

### 3. Vismodegib for the treatment of metastatic or locally advanced basal cell carcinoma

#### Application

- 3.1. The Committee reviewed an application for the treatment of adult patients with metastatic or locally advanced basal cell carcinoma where surgery and/or radiation therapy are not appropriate.

#### Recommendation

- 3.2. The Committee **recommended** that the application for vismodegib in the treatment of adults with metastatic or locally advanced basal cell carcinoma where surgery and/or radiation therapy are not appropriate be **declined**.
- 3.3. The Committee **recommended** the application for vismodegib be referred to the Cancer Treatment Subcommittee for advice regarding alternative treatment options for the proposed population; defining a patient population who could most benefit from treatment with vismodegib if new information led to a more favourable balance of costs, adverse effects, and benefits; and the likely number of patients.
- 3.4. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

#### Information Reviewed

- 3.5. The application with all documentation provided by the applicant
- 3.6. The following additional information:
- [minute of PTAC's previous consideration of vismodegib for Gorlin's Syndrome](#)
  - [NICE TA489](#)
  - [PBAC PSD November 2016 for vismodegib](#)

#### Discussion

- 3.7. The Committee noted that funding for vismodegib as a treatment of basal cell carcinoma (BCC) in patients with Gorlin Syndrome (also known as nevoid BCC syndrome) has been previously considered by PTAC at its meeting in May 2015. At that meeting, PTAC recommended that the application be declined based on weak strength and quality of evidence, concerns at the level of treatment limiting toxicity, very high cost, and no clinically sound reason to limit funding to just Gorlin syndrome patients.
- 3.8. The Committee noted that the supplier had submitted an updated application for vismodegib for the treatment of adult patients with metastatic (mBCC) or locally advanced basal cell carcinoma (laBCC) where surgery and/or radiation therapy are not appropriate.

- 3.9. The Committee noted that BCC was the most common cancer in New Zealand, affecting approximately 50,000 patients per year, with risk factors predominantly being sun exposure, light skin and immunosuppression. Members noted that BCC is rarely fatal with most patients effectively cured with cryotherapy, electrodesiccation and curettage (ED&C), surgical excision, topical 5-fluorouracil or imiquimod, radiation therapy (RT), and photodynamic therapy.
- 3.10. The Committee noted that for patients who develop laBCC or mBCC, treatment options are limited primarily to platinum-based chemotherapy, with reported median survival figures ranging from 6 months to 3.6 years.
- 3.11. The Committee noted that vismodegib is a small-molecule inhibitor of SMO involved in the hedgehog signalling pathway which transmits information to embryonic cells required for cell differentiation. Members noted that SMO mutations are acquired over time with vismodegib treatment.
- 3.12. The Committee noted that the primary evidence for use of vismodegib for the treatment of mBCC and laBCC is from two single-arm, non-comparative phase II studies: ERIVANCE (Sekulic et al. NEJM. 2012;366:2171-9; Sekulic et al. J Am Acad Dermatol. 2015;72:1021-6; Sekulic et al. BMC Cancer 2017;17:332) and STEVIE (Basset-Seguín et al. Lancet Oncol 2015;16:729-36).
- 3.13. The Committee noted that in the final update of the long-term safety and efficacy from the ERIVANCE study (Sekulic et al. BMC Cancer 2017;17:332) that at the time of data cut-off (39 months after completion of accrual) 24 of 33 mBCC patients had progressed, as judged by investigator assessment, or died within 30 days of the last treatment. The median investigator-assessed PFS was 9.3 months for mBCC and 12.9 months for laBCC.
- 3.14. The Committee noted that, as these trials were non-comparative and did not include a control arm or placebo group, the clinical effect of vismodegib was uncertain. Further, that it was difficult to determine durability of response, even for those patients that achieved complete response, and any overall survival (OS) gains in the treated population compared with those who did not receive vismodegib.
- 3.15. The Committee considered that overall the evidence for vismodegib in the treatment of mBCC and laBCC was early, with long-term comparative outcomes on OS or quality of life (QOL) unclear.
- 3.16. The Committee considered that vismodegib treatment was associated with significant adverse event profile that would significantly impact quality of life. Members noted that in clinical practice intermittent dosing schedules were being used to mitigate for toxicity, although considered there was limited evidence for this approach being primarily from the MIKIE trial - a randomised, regimen-controlled, double-blind, phase 2 trial of two intermittent vismodegib dosing regimens in 229 patients with multiple BCC (Dreno et al. Lancet Oncol. 2017;18:404-12) .
- 3.17. Members noted it was uncertain whether funding of vismodegib would result in any offsets from reduced surgery or radiotherapy, as the supplier's requested group is those patients for whom RT or surgery would be inappropriate.
- 3.18. The Committee noted that as funding was requested for a population who were contraindicated to surgery, surgery was not an appropriate comparator. However, the Committee considered there was significant uncertainty regarding how to appropriately define a population that would be truly contraindicated for surgery. Members noted that micrographic surgery often provides improved outcomes including cure for laBCC, however currently access to this in New Zealand was not widespread and patients had to travel.
- 3.19. The Committee considered that it appeared that vismodegib has a biological effect. It considered there could be a place for its use in some individuals with extreme disease, such as where further surgery would result in loss of eyesight or a limb, or where tumours were eroding into a body cavity, cranial vault or nerve invasion resulting in chronic pain. However, the Committee considered that there was no

- evidence to support its use in these settings. Further the effectiveness of vismodegib in these settings on QOL or OS was unknown.
- 3.20. The Committee considered it was difficult to appropriately define access criteria to target funding to an extreme patient group that would also limit use in patients who could undergo less extensive or risky surgery. Members considered that, if funding for vismodegib were to be progressed, then a multidisciplinary approach would be important that included oncology, surgical and radiotherapy expertise. Members also considered a funding mechanism would likely need to allow for consideration of individual circumstances.
  - 3.21. The Committee noted that NPPA applications had previously been received for use of vismodegib for a defined course of treatment for patients who had extensive and unresectable disease where the intention was to reduce tumour size to allow for further surgery. However, the Committee considered that no evidence had been reviewed by PTAC to support the use of vismodegib treatment in this way. Members considered that defining clinically appropriate objective endpoints for withdrawal of vismodegib treatment prior to disease progression in this setting would be challenging.
  - 3.22. The Committee noted that supplier had estimated up to 20 patients per year in the requested patient population would be eligible for treatment (based on the number of patients treated in Australia). However, it noted that this was the same number that had been stated in the 2015 submission for Gorlin syndrome patients only. Members considered that the number of patients who may seek treatment with vismodegib was uncertain, although likely lower than 50 patients per year, and would largely depend on how eligibility criteria were defined.
  - 3.23. The Committee noted that the PBAC had recommended the listing of vismodegib for the treatment of mBCC or laBCC inappropriate for surgery and curative radiotherapy. However, PBAC had noted that whilst there was likely to be benefit from vismodegib for a highly selected patient group, there was significant toxicity associated with vismodigib and no improvement in quality of life.
  - 3.24. The Committee noted that in November 2017 NICE had not recommended vismodegib for the treatment of symptomatic mBCC or laBCC that is inappropriate for surgery or radiotherapy, due to what NICE considered to be uncertainty in the evidence and lacking cost effectiveness. In making this recommendation, NICE had noted that overall survival data from clinical trials in people with laBCC are limited, only a small number of people with mBCC were included in trials, and there are no trials directly comparing vismodegib with best supportive care.

#### 4. **Dexrazoxane for cardioprotection in conjunction with anthracycline chemotherapy**

##### Application

- 4.1. The Committee reviewed the funding of dexrazoxane for cardioprotection in conjunction with anthracycline chemotherapy in children and young adults.

##### Recommendation

- 4.2. The Committee **recommended** that dexrazoxane be funded with low priority for cardioprotection in conjunction with anthracycline chemotherapy in children and young adults subject to the following Special Authority criteria:

Initial application - only from a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Patient is to receive treatment with high dose anthracycline given with curative intent; and
2. Based on current treatment plan, patient's cumulative lifetime dose of anthracycline will exceed 250mg/m<sup>2</sup> doxorubicin equivalent or greater.

- 4.3. The Committee considered the proposed Special Authority should be reviewed by the Cancer Treatments Subcommittee.

- 4.4. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

#### Information Reviewed

- 4.5. The Committee considered the following information:
- [minutes from PTAC August 2017 meeting relating to dexrazoxane](#)
  - [minutes from Cancer Treatment Subcommittee March 2017 meeting relating to dexrazoxane](#)
  - [Asselin et al. JCO 2015;34:854-62](#)
  - [Chow et al. JCO 2015;33:2639-45](#)
  - [Seif et al. Pediatr Blood Cancer 2015;62:704-9](#)

#### Discussion

- 4.6. The Committee noted that the funding of dexrazoxane for cardioprotection in conjunction with anthracycline chemotherapy in children and young adults had been considered by both PTAC and CaTSoP on a number of occasions.
- 4.7. The Committee noted that PTAC's most recent consideration was in May 2013 when it had recommended funding of dexrazoxane for paediatric cancer patients participating in a randomised clinical trial, despite considering dexrazoxane itself to have no clear benefit and some evidence of potential harm in terms of a potential increased relative risk of secondary malignancies.
- 4.8. The Committee noted that in May 2013 PTAC had also recommended that the funding of dexrazoxane for adult patients and for paediatric cancer patients not participating in a randomised clinical trial, including those treated as per trial protocols, be declined.
- 4.9. The Committee noted that at its meeting in March 2017, CaTSoP had again considered funding of dexrazoxane in light of updated evidence for its use in children and young adults; and recommended dexrazoxane be funded for cardioprotection in conjunction with anthracycline chemotherapy in children and young adults who are not participating in a randomised clinical trial, with a medium priority. PTAC noted that Subcommittee members considered the updated evidence addressed safety concerns, but noted that the priority was influenced by uncertainty regarding the long-term clinically meaningful benefit and harm of dexrazoxane in this population.
- 4.10. The Committee noted that there is currently an exception to the HML in place that allows each DHB to decide regarding its use of dexrazoxane in children who are enrolled in a Children's Oncology Group trial.
- 4.11. The Committee noted that the cardiac toxicity of anthracyclines is well established and is the basis for the restrictions on cumulative lifetime anthracycline doses.
- 4.12. The Committee noted that CaTSoP considered that anthracycline cardiotoxicity was now a less significant issue for adults with the change in clinical practice to use shorter courses of anthracyclines than it was 20 or 30 years ago, when the main trials into the use of dexrazoxane were undertaken. However, anthracycline-induced cardiotoxicity remained a significant clinical issue with long-term consequences for paediatric oncology. The Committee noted that high dose anthracycline treatment with cumulative doses in excess of 250 mg/m<sup>2</sup> is important in the treatment of several childhood malignancies and there is a correlation with higher rate of cardiac risk in these populations.
- 4.13. The Committee noted there are various strategies for diminishing cardiovascular risk in adults, such as modified dose schedules and cardiovascular prophylaxis, but there appears to be a lack of evidence for their use in children.
- 4.14. The Committee noted concerns cited in previous minutes regarding decreased efficacy of oncological treatment as a risk of dexrazoxane cotreatment, but considered

- that currently published evidence indicated there was no difference in oncological response rate or overall survival (OS) between dexrazoxane and control arms.
- 4.15. The Committee considered that evidence indicated the rates of infection, haematological toxicity, and CNS toxicity did not appear to differ between patients who received dexrazoxane or not, but it was difficult to separate the acute impact of dexrazoxane from the toxic chemotherapy it is given with.
  - 4.16. The Committee considered that 3-year echocardiography data from Asselin et al. reported statistically significant differences in echocardiogram measurements in relation to dexrazoxane treatment or not. However the Committee noted there was a large amount of unexplained missing data in this paper and there was no material provided that linked the differences in echocardiogram measurements to adverse clinical events.
  - 4.17. The Committee noted the possibility of increased secondary malignancies with the use of dexrazoxane had previously been raised. The Committee noted that Chow et al. 2015 aggregated the overall and cause-specific mortality and original disease relapse data from three studies; and reported over a median follow-up of 12.6 years the proportion of relapses and deaths due to original cancer, second cancer or other cause did not differ significantly by treatment status.
  - 4.18. The Committee considered risk of development of secondary malignancy with the use of dexrazoxane, and the relationship of this to other treatments administered, is uncertain.
  - 4.19. The Committee noted that dexrazoxane is not approved for use in Europe for children under the age of 16 years due to safety concerns primarily around secondary malignancy, however, in the USA there is no restriction on the use of dexrazoxane in children where it is routinely used in Children's Oncology Group trials using anthracyclines.
  - 4.20. The Committee considered that, based on the currently available evidence, there was some evidence that dexrazoxane may have an effect on rates of echocardiogram-based measurements of cardiac function, however the Committee noted that some of these estimates may be biased and the evidence was of low quality and that the long-term outcomes remained unclear.
  - 4.21. The Committee considered that there was good evidence of no impact on event-free survival and OS over the timeframes studied.
  - 4.22. The Committee considered that, due to the delay in emergence of cardiovascular disease, there was a need to continue to follow-up paediatric populations treated with dexrazoxane, and that it appeared further data would be published in the next 5 years.
  - 4.23. The Committee considered the mechanism of action of dexrazoxane to be dependent on the cardiotoxic treatment (anthracycline) being administered and not the neoplastic disease being treated, although the tumour type would likely be an indicator of the intended dose of anthracycline.

## 5. Venetoclax for the treatment of relapsed/refractory CLL and relapsed/refractory 17p deletion CLL

### Applications

- 5.1. The Committee reviewed two supplier applications for Venetoclax for the treatment chronic lymphocytic leukaemia (CLL). These applications were for the indications of relapsed or refractory CLL with no other suitable treatment options and relapsed or refractory CLL with 17p deletion.

### Recommendations

- 5.2. The Committee recommended that the application for Venetoclax in the treatment of relapsed or refractory CLL with no other suitable treatment options be **deferred** until additional data regarding survival and quality of life is available.
- 5.3. The Committee recommended that the application for Venetoclax in the treatment of relapsed or refractory CLL with 17p deletion be **deferred** until additional data regarding survival and quality of life is available.
- 5.4. The Committee recommended that the Cancer Treatment Subcommittee review the applications once new data is received, prior to it being resubmitted to the Committee.
- 5.5. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Information Reviewed

- 5.6. The application and all additional documentation provided by the applicant. PTAC noted that the full clinical study report for M14-032 was in excess of 20,000 pages long and that it was not feasible to review this in any detail.
- 5.7. The following additional information:
  - collated PTAC and CaTSoP minutes [for ibrutinib](#)
  - [RESONATE \(Byrd et al. NEJM, 2014;371:213-23\)](#)
  - [RESONATE-2 \(Burger et al. NEJM 2015;373\(25\):2425-37\)](#)
  - [RESONATE-17 \(O'Brien et al. Lancet Oncol 2016;17:1409-18\)](#)
  - [NICE \(2017\) venetoclax for CLL](#)
  - [Furman et al. N Engl J Med. 2014;370:997-1007](#)
  - [Jones et al. Lancet Oncol. 2017;19:65-75](#)
  - [Seymour et al. 2017](#) interim analysis of the Murano Study (late-breaking abstract from the 2017 ASH conference).
  - Letter of support from a number of New Zealand haematologists

### Discussion

- 5.8. The Committee noted that treatments for CLL were evolving quickly driven by an improved understanding of the molecular pathophysiology of CLL. Molecular targets as Brutons tyrosine kinase (BTK), PI3 kinase inhibition and BCL-2 inhibition have been identified and have treatments available. The Committee noted that ibrutinib, idelalisib and venetoclax were available internationally. The Committee noted that these treatments were not currently funded in New Zealand, potentially making comparisons of even newer treatments more difficult in the New Zealand setting.
- 5.9. The Committee noted the following statement was included in the Medsafe data sheet for venetoclax "The indications are approved based on overall response rates. Duration of response and improvements in overall survival, progression-free survival or health-related quality of life have not been established".
- 5.10. The Committee noted the Phase II M14-032 trial ([Jones et al. Lancet Oncol. 2018;19:65-75](#)) of venetoclax in patients with relapsed/refractory CLL after B-cell receptor signalling pathway inhibitor treatment. The Committee noted patients could have received ibrutinib or idelalisib previously, but were enrolled based on the therapy

- used most recently. The Committee considered the response rates appeared high, but the evidence for benefit was limited by the small sample sizes (despite the protocol amendment to add additional patients) and immature follow-up data. The Committee considered the estimates of PFS must be extremely uncertain given the relative proportions of progression at time of data cut-off.
- 5.11. The Committee noted that CLL patients with 17p deletion or TP53 mutations have fewer currently funded treatment options and generally have a worse prognosis and poorer response to therapy compared with CLL patients without these genetic mutations.
  - 5.12. The Committee noted the single-arm Phase II M13-982 trial ([Stilgenbauer et al. Lancet Oncol. 2016;17:768-78](#)) of venetoclax in patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion.
  - 5.13. The Committee compared the evidence for venetoclax in the 17p deletion population with that reviewed by the Committee for ibrutinib at previous meetings, primarily RESONATE-17 ([O'Brien et al. Lancet Oncol. 2016;17:1409-18](#)). The Committee considered the analysis of data for venetoclax from the presented data was not as mature as the data reviewed for RESONATE-17, in particular with insufficient follow up duration, survival outcomes and quality of life data.
  - 5.14. The Committee noted there is no comparative trials between venetoclax and ibrutinib, although the international clinical experience with ibrutinib is more extensive.
  - 5.15. The Committee noted correspondence from haematologists who suggested that it would be reasonable to use venetoclax monotherapy in newly diagnosed patients with TP53 mutations or 17p deletion, given the few effective funded treatment options at present.
  - 5.16. The Committee noted no trials are planned for venetoclax monotherapy in newly diagnosed patients with TP53 mutations or 17p deletion, although the CLL14 Phase 3 trial assessing the use of venetoclax in combination with obinutuzumab in front-line CLL for a fixed treatment duration of 12 months which will include some patients with TP53 mutations and 17p deletions, is due in 2019.

## 6. Levonorgestrel Intrauterine System for contraception

### Application

- 6.1. The Committee reviewed the applications for levonorgestrel intrauterine system for contraception.

### Recommendation

- 6.2. The Committee recommended that levonorgestrel intrauterine system (LIUS) for contraception be listed with a **high priority**.
- 6.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Information Reviewed

- 6.4. The applications with all documentation provided by the applicants.
- 6.5. The following additional information:
  - [Abortion Supervisory Committee \(2015\). Annual Report. Ministry of Justice.](#)
  - [Diedrich et al. Three-year continuation of reversible contraception. American Journal of Obstetrics and Gynecology, 2015;213:662.e1-8.](#)
  - French et al. Hormonally impregnated intrauterine systems (IUSs) versus other forms of reversible contraceptives as effective methods of preventing pregnancy. Cochrane Database Syst Rev 2004;(3):CD001776.
  - [Kavanaugh et al. Changes in Use of Long-Acting Reversible Contraceptive Methods Among U.S. Women, 2009–2012. Obstetrics and Gynecology. 2015;126:917-27.](#)

- [Krashin et al. Hormonal and intrauterine methods for contraception for women aged 25 years and younger. Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD009805. DOI: 10.1002/14651858.CD009805.pub3.](#)
- [Lawton et al. E Hine: access to contraception for indigenous Māori teenage mothers J Primary Health Care. 2016;8:52-9.](#)
- Luukkainen et al. Effective contraception with the levonorgestrel-releasing intrauterine device: 12-month report of a European multicenter study. *Contraception* 1987;36:169-79.
- Mishal J. Intrauterine devices: mechanisms of action, safety, and efficacy. *Contraception* 1998;58(3 Suppl):45S-53S
- Morton et al. Growing up in New Zealand: A longitudinal study of New Zealand children and their families. Report 2: Now we are born. Auckland: Growing Up in New Zealand, 2012.
- NICE Guidelines 2014. Long-acting reversible contraception.
- [Petta et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum Reprod. 2005;20:1993-8.](#)
- Roke et al. New Zealand women's experience during their first year of Jadelle® contraceptive implant. *J Primary Health Care*. 2016;8:13-9
- Rose et al. Uptake and adherence to long-acting reversible contraceptive post-abortion. *Contraception* 2010;82(4):345-53
- Sandle & Tuohy. 'Everyone's talking Jadelle': the experiences and attitudes of service providers regarding the use of the contraceptive implant, Jadelle in young people in New Zealand. *NZMJ* 2017;130:40-6.
- [Secura et al. The Contraceptive CHOICE Project: reducing barriers to long-acting reversible contraception. Am J Obstet Gynecol 2010;203:115.e:111-17.](#)
- Sivin et al. Long-term contraception with the Levonorgestrel 20 mcg/day (LNG-IUS) and the Copper T 380Ag intrauterine devices: a five-year randomized study. *Contraception* 1990;42:361-78.
- [Statistics NZ 2003. Teenage Fertility in New Zealand.](#)
- Soriano et al. Use of long-acting reversible contraceptives in the UK from 2004 to 2010: analysis using The Health Improvement Network Database. *Eur J Contracept Reprod Health Care* 2014;19:439-47.
- Trussell J. Contraceptive failure in the United States. *Contraception* 2011;83:397-404.
- [Varma et al. The effectiveness of a levonorgestrel-releasing intrauterine system \(LNG-IUS\) in the treatment of endometrial hyperplasia – a long term follow-up study. Eur J Obstet Gynecol Reprod Biol. 2008;139:169-75.](#)

## Discussion

- 6.6. The Committee considered funding applications from four health professional organisations for levonorgestrel intrauterine system for the indication of contraception for women of reproductive age. The applications were from Family Planning New Zealand, the New Zealand Nurses Organisation, the Royal New Zealand College of General Practitioners, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.
- 6.7. The Committee noted that the currently funded forms of contraceptives used in the New Zealand market are condoms, oral contraceptives (both combined and progestogen only), medroxyprogesterone injection, levonorgestrel subdermal implant, and copper intrauterine devices (IUD).
- 6.8. The Committee noted that long-acting reversible contraception (LARC) includes LIUS, copper IUS and levonorgestrel subdermal implant; LARC does not include medroxyprogesterone depot injection.
- 6.9. Members noted that while LIUS is not funded for contraception in New Zealand, approximately 8,000 of women are choosing to self-fund LIUS.

- 6.10. The Committee noted that there are also two other Medsafe approved brands of LIUS: Levosert (52 mg levonorgestrel) is approved for the indications of contraception and treatment of idiopathic menorrhagia for up to three years, and Jaydess (13.5 mg levonorgestrel) is indicated for up to three years of contraception.
- 6.11. The Committee noted that the funding applications were reviewed by the Reproductive and Sexual Health Subcommittee of PTAC at their April 2017 meeting. The Committee noted that Subcommittee recommended LIUS be listed on the Pharmaceutical Schedule, with a high priority, as a contraception option for women of reproductive age who are unable to use (due to contraindications) or tolerate (due to side effects) other long-acting reversible contraception (LARC).
- 6.12. The Committee noted that contraception is not viewed as a disease by the medical community, and noted the National Institute for Health and Care Excellence (NICE) 2014 Guidelines on Long-acting Reversible Contraception advise that women requiring contraception should be given information about and offered a choice of all methods, including LARC.
- 6.13. On Health Need, Health Benefits, and Suitability, the Committee noted that people's quality of life is increased by a sense of control over their fertility. The Committee noted other benefits raised by applicants, which included social benefits; reduction in unwanted pregnancies, tolerability, and reversibility.
- 6.14. The Committee noted that the general abortion rate in New Zealand has been declining since 2004 and while this may be due to increasing LARC use, youth behavioural change is also a likely contributor.
- 6.15. The Committee noted that the WHO's effectiveness rates for contraceptives is based on Trussell (2011), which is noteworthy as it reflects typical use, rather than perfect use data. The Committee noted that LARC is the most effective of the contraceptive methods, and superior to the depot injection, oral pill and barrier methods.
- 6.16. The Committee noted the Luukkainen et al. (1987) and Sivin et al. (1990) studies comparing the LIUS and copper IUD. The Committee noted that the contraception efficacy rates were found to be similar. The Committee noted this was supported by the French et al. (2004) Cochrane review.
- 6.17. The Committee noted that the adverse effects of LIUS were similar to the copper IUD in terms of uterine perforation risk, pelvic inflammatory disease and menstrual bleeding pattern Members noted while some women see amenorrhoea as a benefit, amenorrhoea is not always viewed as desirable as some women find regular menstrual bleeding to be a reassuring biological process.
- 6.18. The Committee noted the Roke et al. (2016) NZ study using the levonorgestrel subdermal implant, where 18% of the 252 women had the implant removed within one year; over half of the removals were due to unwanted bleeding irregularities. However, the Committee noted there was a high loss (20%) to follow-up in this study, which meant the bias in this estimate of reason for removal was uncertain.
- 6.19. The Committee noted the Mishal (1998) study reported that copper IUDs can increase menstrual blood loss by 50%, making these contraceptives unsuitable for women with heavy or painful periods.
- 6.20. The Committee noted that the Secura et al. (2010) CHOICE study comprised mostly adults (96% women were over 18 years of age) and 45.1% had a history of abortion. The Committee also noted that the participants were involved in up to two hours of discussion during enrolment and that the study investigators had a clear goal of promoting LARC. Members considered that all these factors would have significantly influenced the participants' decisions about contraception and likely increased bias towards LARC as the contraceptive of choice. The Committee noted that 67% chose a LARC: 47% LIUS, 9% copper IUD, and 11% subdermal implant.
- 6.21. The Committee noted the Diedrich et al. (2015) 3-year follow-up of the CHOICE study, which showed almost identical continuation rates for LIUS (69.8%) and copper IUD (69.7%), and similar rates for the subdermal implant (56.2%), compared to oral

- contraceptives (31.5%). Members noted that LARC continuation rates at three years were 52.6% for 14-19 year olds, and 69.2% for 20-45 year olds.
- 6.22. The Committee noted the Rose et al. (2010) NZ study where LIUS, copper IUD or medroxyprogesterone depot were offered post-termination of pregnancy. Members noted the six-fold increase in uptake of LIUS in this patient group, and noted that the subdermal implant was not an available option. The Committee noted continuation rates at six months were 81% for LIUS, 74% for copper IUD and 71% for medroxyprogesterone depot.
- 6.23. The Committee noted the qualitative NZ study by Lawton et al. (2016) of 41 Māori teenage mothers' experiences in accessing contraception, which identified significant system and clinical barriers especially in regard to LARC. Members considered that these access barriers would likely persist if LIUS were to be funded for contraception.
- 6.24. The Committee noted the Cochrane Systematic Review by Krashin et al. (2015) comparing contraceptive failure (pregnancy) rates and contraception continuation rates for hormonal and intrauterine contraception among women aged 25 years and younger. The Committee noted that five randomised control trials met the review inclusion criteria, of which only three used LIUS as a comparator:
- Godfrey et al. *Contraception* 2010;81:123-7
  - Nelson et al. *Obstet Gynecol* 2013;122:1205-13
  - Suhonen et al. *Contraception* 2004;69:407-12.
- 6.25. The Committee noted that the Godfrey et al. (2010) trial of 23 women compared the copper IUD with the LIUS 20 µg/day with only one pregnancy occurring (which was in the copper group). Members noted that six-month continuation rates favoured LIUS (75% vs 45% for copper IUD), the confidence intervals were very wide (OR 3.6 CI 0.62-21.03). Members noted that bleeding problems were the reason for discontinuation by one woman in each group; and in the copper IUD group, other reasons for discontinuation were excessive cramping and expulsion.
- 6.26. The Committee noted that the Nelson et al. (2013) trial of 2884 women compared LIUS 12 µg/day (LNG-IUS 12) with 16 µg/day (LNG-IUS 16). Unadjusted Pearl Indices were similar: 0.22 for LIUS 12 and 0.21 for LIUS 16 at one year; and at three years, 0.36 and 0.17, respectively. Members noted that the risk of expulsion was 4.78% overall, and two cases of pelvic inflammatory disease were reported. The Committee noted that 22% of women discontinued the LIUS due to adverse events; however, overall continuation was not stated.
- 6.27. The Committee noted that the Suhonen et al. (2004) trial of 200 women compared LIUS 20 µg/day with the combined oral contraceptive (COC) and found no important differences in pregnancy rates or continuation rates. No pregnancies occurred in either group over 12 months. Twelve-month continuation rates were 80% for LIUS and 73% for COC. Members noted that women in the LIUS group were more likely than women in the COC group to discontinue their method of contraception because of pain, and less likely to discontinue because of personal reasons. In the LIUS group, four out of six discontinuations were due to pain and occurred within the first three months after insertion.
- 6.28. The Committee noted that Krashin et al. (2015) concluded the current evidence was insufficient to compare efficacy and continuation rates for hormonal and intrauterine contraceptive methods in women aged 25 years and younger. The Committee considered the evidence from this RCT to be weak.
- 6.29. The Committee noted the UK study by Soriano et al. (2014) of LARC use in primary care between 2004 and 2010, which showed that use of the copper IUD and depot injection has declined and uptake of the subdermal implant and LIUS has increased. Members noted, however, that increased uptake of the subdermal implant was highest among younger women and that LIUS use was higher in women aged 35 years and older. The Committee considered that a similar age-group pattern of uptake may occur in NZ if LIUS were to be funded for contraception.

- 6.30. The Committee considered that LIUS is an effective LARC that provides a further choice for women seeking long-acting contraception and its main therapeutic benefit is a reduction in heavy menstrual bleeding. Members considered the contraceptive efficacy of LIUS to be similar to the copper IUD and levonorgestrel subdermal implant; and better than oral or injectable contraceptives in terms of mitigating adherence issues.
- 6.31. The Committee considered that there is an unmet health need for women whom the subdermal implant and copper IUD are clinically inappropriate (due to heavy menstrual bleeding or painful periods).
- 6.32. The Committee considered that there is high quality, strong evidence for efficacy of LIUS in preventing pregnancy and good continuation rates, however, members noted that the evidence for use in women under 25 years of age is weak in strength and of poor quality. The Committee considered that uptake of LIUS as a contraceptive may be lower in young women. This is further supported by members advising that in primary care fewer vaginal speculum examinations are being conducted and cervical screening not being initiated until women are 25 years old, resulting in younger women being exposed to fewer gynaecological procedures and potentially less accepting of intrauterine forms of contraception.
- 6.33. The Committee noted the number of LIUS being used in NZ, of which just over half are funded with the remainder (about 8,400) either being provided by DHB hospitals outside of the pharmaceutical budget or self-funded by women. Members considered that most women who have a high clinical need for LIUS are already using LIUS. The Committee noted that it would be reasonable to expect an extra 10,000 women per year to be eligible for funded LIUS if it were listed for contraception for all women. This would include replacement LIUS for women currently receiving LIUS outside the Pharmaceutical Schedule.
- 6.34. The Committee noted that suitability was a key factor with LIUS as its use requires patients to have access to trained inserters. However, members considered that it is relatively easy to teach and learn how to insert LIUS in primary care.
- 6.35. The Committee considered that it would be clinically acceptable to fund either a three-year or five-year LIUS, and that any brand would be suitable. The Committee noted that training requirements would be the same regardless of brand.
- 6.36. The Committee noted that the cost of the insertion procedure would remain a potential access barrier if LIUS were to be funded for contraception. The Committee also noted that all LARC require up to three medical appointments: the first to discuss options, the second to insert the device, and a third appointment for follow-up purposes, and that these would be an additional cost to women seeking a LARC.
- 6.37. The Committee considered that LIUS for contraception should be listed without restriction.

## 7. Levonorgestrel Intrauterine System widening access for the treatment of endometriosis

### Applications

- 7.1. The Committee reviewed the applications for levonorgestrel intrauterine system in the treatment of endometriosis.

### Recommendation

- 7.2. The Committee recommended that Levonorgestrel Intrauterine System (LIUS) for the treatment of endometriosis in the community setting be listed with a **high priority**.
- 7.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Information Reviewed

- 7.4. The applications with all documentation provided by the applicants.

7.5. The following additional information:

- [Brown & Farquhar. Endometriosis: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD009590](#)
- [Morassutto et al. Incidence and estimated prevalence of endometriosis and adenomyosis in Northeast Italy: a data linkage study. PLoS One. 2016;11: e0154227](#)
- National Institute for Health and Care Excellence (NICE). Endometriosis: diagnosis and management 2017. <https://www.nice.org.uk/guidance/ng73>
- [Soini et al. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol. 2014;124:292-9.](#)

## Discussion

7.6. The Committee considered funding applications from two health professional organisations for levonorgestrel intrauterine system (LIUS) to be funded in the community for endometriosis. The applications were from the Royal New Zealand College of General Practitioners, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

7.7. The Committee noted that the funding applications were reviewed by the Reproductive and Sexual Health Subcommittee of PTAC at their April 2017 meeting. The Committee noted the Subcommittee recommended that LIUS access be widened in the community, with a high priority, for women with endometriosis.

7.8. The Committee noted that LIUS 20mcg/day is currently funded for endometriosis in hospital, subject to the following restrictions:

**Initiation (endometriosis)** only from an obstetrician or gynaecologist for patients meeting the following criterion:

1.1 The patient has a clinical diagnosis of endometriosis confirmed by laparoscopy.

**Continuation (endometriosis)** only from an obstetrician or gynaecologist for patients meeting the following criteria:

Either:

1.1 Patient demonstrated satisfactory management of endometriosis; or

1.2 Previous insertion was removed or expelled within 3 months of insertion.

**Note:** Endometriosis is an unregistered indication.

7.9. The Committee noted there is a range of funded pharmaceuticals that can be used for endometriosis; these include NSAIDs, oral contraceptives, depot medroxyprogesterone and oral progestogens. Members also noted that gonadotropin-releasing hormones are funded and used to manage endometriosis.

7.10. The Committee noted that while endometriosis is common, it is difficult to quantify prevalence as it can be asymptomatic, symptoms can vary and be non-specific, and definitive diagnosis can require direct visualisation of culprit lesions during open surgery or laparoscopy and/or biopsy, which are invasive procedures. The Committee noted that pelvic pain is a key characteristic of endometriosis and is often the primary presenting symptom that patients seek medical help. Members also considered that unresolved pelvic pain can develop into chronic pain with consequent poor prognosis.

7.11. The Committee noted the Brown et al. (2014) review of Cochrane systematic reviews for endometriosis, which showed evidence of a significant decrease in recurrence of painful menstruation in the LIUS group compared with the expectant management group (RR 0.22, 95% CI 0.08 to 0.60) in two trials (n = 95 women). Members also noted that in a third trial (n = 40) there was no evidence of significant difference in pain scores between the LIUS group and women who received gonadotropin-releasing hormones. The Committee considered that the trial numbers in the review were low.

7.12. The Committee noted the Soini et al. (2014) study that found a reduced incidence of endometrial, pancreatic and lung cancers with use of LIUS for menorrhagia but an

- increased incidence of breast cancer. Members noted the author's conclusion that levonorgestrel-releasing intrauterine system may have a protective effect against endometrial malignant transformation. Members noted this study was about use of LIUS for menorrhagia, rather than endometriosis. While the Committee considered that this study is likely to be generalisable to NZ, the study design overlooked confounding factors such as parity, family history and other hormone use.
- 7.13. The Committee noted that the NICE clinical guideline on endometriosis (2017) recommends hormonal therapy (for example, the combined oral contraceptive or a progestogen) as an option for women with suspected, confirmed or recurrent endometriosis. Members also noted that the advice appears to be intentionally non-specific about which hormonal treatment; and further that the guideline advises that if initial hormonal treatment is not effective, not tolerated or is contraindicated, the patient should be referred to secondary services for investigation.
  - 7.14. The Committee noted that in New Zealand, expert opinion and clinical practice supports the use of LIUS in primary care as both a trial intervention and diagnostic for endometriosis to reduce the burden on secondary care, in particular laparoscopy services. Members noted that this is consistent with the NICE 2017 guideline.
  - 7.15. The Committee considered that there is an absence of good randomised controlled evidence for LIUS and comparators, including surgery, in the primary treatment of endometriosis. However, members noted that anecdotal evidence, expert opinion and clinical practice nationwide in the O&G discipline supports the use of LIUS for endometriosis, and suggests it is effective for managing the symptoms of endometriosis, especially cyclical pain.
  - 7.16. The Committee considered that there may be an unmet health need for women with chronic pelvic pain due to endometriosis and women with heavy menstrual bleeding who are unable to use copper IUD.
  - 7.17. The Committee noted that the evidence for the health need of endometriosis is mixed. For period pain, the Committee considered that the evidence is of moderate quality but weak strength for clinical improvement. The Committee noted moderate evidence for the reduction of long term cancer risk. The Committee also noted that the evidence for improvement of any other endometriosis symptoms is of poor quality and weak strength.
  - 7.18. The Committee noted that use of LIUS for endometriosis is not a registered indication, however, members acknowledged that there is an established clinical use in NZ hospitals and it would be reasonable to fund LIUS in the community by listing it in Section B of the Pharmaceutical Schedule.
  - 7.19. The Committee noted that widening access to LIUS for endometriosis in the community would increase demand for access to trained inserters in primary care. However, members considered that it is relatively easy to teach and learn how to insert LIUS in primary care.
  - 7.20. The Committee considered that it would be clinically acceptable to fund either a three-year or five-year LIUS, and that any Medsafe approved brand would be suitable. The Committee noted that training requirements would be the same regardless of brand.

## 8. Levonorgestrel Intrauterine System for the treatment of endometrial hyperplasia without atypia

### Application

- 8.1. The Committee reviewed the applications for levonorgestrel intrauterine system in the treatment of endometrial hyperplasia without atypia.

### Recommendation

- 8.2. The Committee recommended that Levonorgestrel Intrauterine System for the treatment of endometrial hyperplasia without atypia be listed with a **high priority**.
- 8.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Information Reviewed

- 8.4. The applications with all documentation provided by the applicants.
- 8.5. The following additional information:
  - Abu Hashim H, Ghayaty E, El Rakhawy M. Levonorgestrel-releasing intrauterine system vs oral progestins for non-atypical endometrial hyperplasia: a systematic review and metaanalysis of randomized trials. *Am J Obstet Gynecol*. 2015;213:469-78.
  - [Brown & Farguhar. Endometriosis: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD009590](#)
  - [Luo et al. Levonorgestrel-releasing intrauterine system for atypical endometrial hyperplasia. Cochrane Database of Systematic Reviews 2013, Issue 6.](#)
  - Morassutto et al. Incidence and estimated prevalence of endometriosis and adenomyosis in Northeast Italy: a data linkage study. *PLoS One*. 2016;11(4):e0154227.
  - [Orbo et al. Levonorgestrel-impregnated intrauterine device as treatment for endometrial hyperplasia: a national multicentre randomised trial. BJOG. 2014;121:477-86.](#)
  - Royal College of Obstetricians and Gynaecologists (UK) 2016 Guideline for the management of endometrial hyperplasia. [https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg\\_67\\_endometrial\\_hyperplasia.pdf](https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg_67_endometrial_hyperplasia.pdf)
  - [Varma et al. The effectiveness of a levonorgestrel-releasing intrauterine system \(LNG-IUS\) in the treatment of endometrial hyperplasia - a long-term follow-up study. Eur J Obstet Gynecol Reprod Biol 2008;139:169-75.](#)

### Discussion

- 8.6. The Committee considered funding applications from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, and the Hawkes Bay DHB, for levonorgestrel intrauterine system (LIUS) to be funded for endometrial hyperplasia without atypia.
- 8.7. The Committee noted that the funding applications were reviewed by the Reproductive and Sexual Health Subcommittee of PTAC at their April 2017 meeting. The Committee noted the Subcommittee recommended that LIUS access be widened, with a high priority, to include endometrial hyperplasia without atypia.
- 8.8. The Committee noted that LIUS 20mcg/day is currently funded (and subject to restrictions) for endometriosis in hospital, but not funded for endometrial hyperplasia without atypia in the community or hospital.
- 8.9. The Committee noted the UK Royal College of Obstetricians and Gynaecologists 2016 guideline for the management of endometrial hyperplasia, which states that the

risk of endometrial hyperplasia without atypia progressing to endometrial cancer is less than 5% over 20 years and that the majority of cases of endometrial hyperplasia without atypia will regress spontaneously. Members noted that the guideline recommends progestogen treatment for women who fail to regress following observation alone and in symptomatic women with abnormal uterine bleeding. The Committee further noted the guideline advises that both continuous oral progestogens and LIUS are effective in achieving regression of endometrial hyperplasia without atypia. LIUS should be the first-line treatment as it has a higher disease regression rate with a more favourable bleeding profile and fewer adverse effects than oral progestogens.

- 8.10. The Committee noted the Abu Hashim et al. (2015) systematic review, which identified seven RCTs of endometrial hyperplasia without atypia. Pooled analysis showed the LIUS achieved a significant therapeutic response compared to oral progestins. Members noted the authors commented this may be due to high concentrations being delivered directly to the uterus. The Committee noted that the group using LIUS had fewer hysterectomies and that there was no difference observed in the rate of irregular vaginal bleeding between the two treatment groups. Members noted the review identified that irregular bleeding can occur in up to 35% of LIUS users during the first three months. The Committee noted that the review found moderate quality evidence for LIUS over oral progestins for endometrial hyperplasia without atypia, and that the authors concluded LIUS should be offered as an alternative to women with this condition.
- 8.11. The Committee noted the Varma et al. (2008) study that found LIUS to be effective for endometrial hyperplasia, irrespective of whether non-atypical or atypical hyperplasia was being treated. Members noted that beneficial effects were observed by most participants within one year of treatment. The Committee noted the study authors considered that use of LIUS to treat non-atypical hyperplasias would likely reduce the number of hysterectomies performed for this condition.
- 8.12. The Committee considered that there was sufficient quality and strength of evidence to support the use of LIUS as a funded option, without restrictions, for endometrial hyperplasia without atypia.
- 8.13. The Committee advised that if PHARMAC needs advice on Special Authority criteria for LIUS for endometriosis hyperplasia, that this be referred to the Reproductive and Sexual Health Subcommittee.
- 8.14. The Committee noted that suitability was a key factor with LIUS as its use requires patients to have access to trained inserters. Members noted that widening access to LIUS for endometrial hyperplasia without atypia would increase demand for access to trained inserters.
- 8.15. The Committee considered that it would be clinically acceptable to fund either a three-year or five-year LIUS, and that any Medsafe approved brand would be suitable. The Committee noted that training requirements would be the same regardless of brand.

8.16.

## 9. Levonorgestrel Intrauterine System widening access for the treatment of heavy menstrual bleeding

### Application

- 9.1. The Committee reviewed the applications for widening access to levonorgestrel intrauterine system for heavy menstrual bleeding.

### Recommendation

- 9.2. The Committee **recommended** that widened access of levonorgestrel intrauterine system for the treatment of heavy menstrual bleeding be listed with a **high priority**.
- 9.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Information Reviewed

- 9.4. The application with all documentation provided by the applicants.
- 9.5. The following additional information:
- [Gupta et al. A randomised controlled trial of the clinical effectiveness and cost-effectiveness of the levonorgestrel-releasing intrauterine system in primary care against standard treatment for menorrhagia: the ECLIPSE trial. Health Technology Assessment 2015;19 \(88\).](#)
  - Blumenthal et al. Cost-effectiveness and quality of life associated with heavy menstrual bleeding among women using the levonorgestrel-releasing intrauterine system. Int J Gynaecol Obstet. 2011;112:171-8.
  - [Marjoribanks et al. et al. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2016\(1\):CD003855.](#)
  - [Middleton et al. Hysterectomy, endometrial destruction, and levonorgestrel releasing intrauterine system \(Mirena\) for heavy menstrual bleeding: systematic review and meta-analysis of data from individual patients. BMJ 2010;341c3919](#)
  - National Institute for Health and Care Excellence (NICE). Heavy menstrual bleeding: assessment and management clinical guideline 2018. <https://www.nice.org.uk/guidance/cg44>
  - [Qiu et al. Levonorgestrel-releasing intrauterine system versus medical therapy for menorrhagia: a systematic review and meta-analysis. Medical Science Monitor 2014;20:1700-13.](#)

### Discussion

- 9.6. The Committee considered funding applications from two health professional organisations for widened access of levonorgestrel intrauterine system (LIUS) for the treatment of heavy menstrual bleeding (HMB). The applications were from the Royal New Zealand College of General Practitioners, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.
- 9.7. The Committee noted that the funding applications were reviewed by the Reproductive and Sexual Health Subcommittee of PTAC at their April 2017 meeting. The Committee noted the Subcommittee recommendation that access to LIUS for HMB be widened, with a high priority, for women with HMB.
- 9.8. The Committee noted that LIUS 20mcg/day is currently funded for HMB in both community and hospital, subject to the following restrictions, respectively:

## Section B of Pharmaceutical Schedule Special Authority for Subsidy – Form SA1608

**Initial application** – (No previous use) only from a relevant specialist or general practitioner. Approvals valid for 6 months for applications meeting the following criteria:  
All of the following:

- 1 The patient has a clinical diagnosis of heavy menstrual bleeding; and
- 2 The patient has failed to respond to or is unable to tolerate other appropriate pharmaceutical therapies as per the Heavy Menstrual Bleeding Guidelines; and
- 3 Either:
  - 3.1 serum ferritin level < 16 mg/l (within the last 12 months); or
  - 3.2 haemoglobin level < 120 g/l.

Note: Applications are not to be made for use in patients as contraception except where they meet the above criteria.

**Renewal** only from a relevant specialist or general practitioner. Approvals valid for 6 months for applications meeting the following criteria:

Both:

- 1 Either:
  - 1.1 Patient demonstrated clinical improvement of heavy menstrual bleeding; or
  - 1.2 Previous insertion was removed or expelled within 3 months of insertion; and
- 2 Applicant to state date of the previous insertion.

## Section H of Pharmaceutical Schedule

**Initiation (heavy menstrual bleeding)** only from an obstetrician or gynaecologist for patients meeting the following criteria:

Both:

- 1 Both of the following:
  - 1.1 The patient has a clinical diagnosis of heavy menstrual bleeding; and
  - 1.2 The patient has failed to respond to or is unable to tolerate other appropriate pharmaceutical therapies as per the Heavy Menstrual Bleeding Guidelines; and

Any of the following:

- 2.1 serum ferritin level < 16 mcg/l (within the last 12 months); or
- 2.2 haemoglobin level < 120 g/l; or
- 2.3 the patient has had a uterine ultrasound and either a hysteroscopy or endometrial biopsy.

**Continuation (heavy menstrual bleeding)** only from an obstetrician or gynaecologist for patients meeting the following criteria:

Either:

- 1.1 The patient demonstrated clinical improvement of heavy menstrual bleeding; or
- 1.2 Previous insertion was removed or expelled within 3 months of insertion.

- 9.9. The Committee noted that a range of other hormonal treatments used in HMB are funded; these comprise combined oral contraceptives, depot or oral medroxyprogesterone, and oral norethisterone. Members also noted that tranexamic acid and NSAIDs are non-hormonal funded treatments that can be used for HMB.
- 9.10. The Committee noted that in addition to Mirena (52 mg levonorgestrel providing 20mcg/day), there is one other Medsafe approved brand of LIUS for HMB: Levosert (52 mg levonorgestrel providing 20mcg/day), which is approved for the indications of contraception and treatment of idiopathic menorrhagia for up to three years.
- 9.11. The Committee noted the National Institute for Health and Care Excellence (NICE) 2018 clinical guideline on heavy menstrual bleeding assessment and management, which advises that patient choice, quality of life and consideration of contraception needs are important aspects of HMB treatment. Members noted that NICE defines HMB as excessive menstrual blood loss that interferes with the woman's physical, emotional, social and material quality of life.
- 9.12. The Committee considered that HMB has a significant impact on quality of life and daily functioning, and in the NZ context HMB can affect women's ability to participate in their community if custom requires them to avoid involvement in certain aspects of social or cultural activities.
- 9.13. The Committee considered that there is an unmet health need in women with neurodevelopmental disorders in whom HMB and normal menstruation causes

- distress. While members considered that this patient group is likely to be small, these women have a high health need and HMB has a major impact on their quality of life.
- 9.14. The Committee noted that in one DHB, the treatment access pathway has been implemented to enable primary care access to LIUS for HMB for women in whom anaemia has been excluded and risk factors such as high BMI are not present. The Committee noted that while this pathway reduced the burden of unnecessary medical investigations, it was creating an access disparity for women in other DHBs.
  - 9.15. The Committee noted that the NICE guideline (2016) recommends if history and investigations indicate pharmaceutical treatment of HMB is appropriate, treatments should be considered in this order: LIUS; tranexamic acid, NSAIDs or combined oral contraceptives; norethisterone or depot progestogens. The Committee also noted that NICE advises at least 12 months use be anticipated when offering LIUS, and that women should be informed of likely changes in menstrual bleeding pattern, particularly in the first few cycles and possibly lasting longer than six months.
  - 9.16. The Committee noted that the reduction in blood loss that occurs with use of NSAID or tranexamic acid for HMB is up to half that seen with LIUS (Marjoribanks et al. 2016).
  - 9.17. The Committee noted the Marjoribanks et al. (2016) Cochrane review of 15 RCTs, which found that hysterectomy, endometrial surgery and LIUS were all effective in reducing HMB, and that these treatments suited most women better than oral medication. Members noted that while surgery was most effective intervention, at least over the short term, it carries greater risks and costs than LIUS. The Committee considered the quality of evidence in this review to be very low to moderate due to attrition, imprecision and lack of blinding.
  - 9.18. The Committee noted the Gupta et al. (2015) RCT, which was not part of the Marjoribanks et al. (2016) Cochrane review. Members noted the 5-year trial showed that LIUS, compared with usual medical therapies, provided greater improvement over two years in women's assessments of the effect of HMB on their daily routine (including work, social and family life), psychological and physical well-being. The Committee noted, however, that by five years, 53% of women in the LIUS group had it removed due to unpredictable bleeding or lack of effectiveness.
  - 9.19. The Committee noted that the Qiu et al. (2014) meta-analysis of eight RCTs found greater reduction in menstrual blood loss with LIUS compared to other standard HMB pharmacological therapies. Members noted this analysis also looked at patient satisfaction and persistence, both of which favoured LIUS.
  - 9.20. The Committee noted that Blumenthal et al. (2011) looked at economic and health-related quality of life outcomes associated with LIUS for HMB. Members noted that irrespective of the measuring instrument used, health-related quality-of-life outcomes were found to be improved to a degree similar to that achieved with endometrial ablation or hysterectomy. The Committee also noted that in some cases LIUS appeared to be more effective and less costly than the surgical options.
  - 9.21. The Committee concluded that the evidence they reviewed supported the applications for widened access to LIUS as an option for all women with HMB, particularly in the primary care setting where LIUS is more cost-effective than surgery. The Committee also noted that the current treatment paradigm gives greater weight to the impact of HMB on quality of life, therefore, the utility of objective blood tests for ferritin or haemoglobin is now redundant for the Special Authority criteria.
  - 9.22. The Committee considered that up to 3,000 additional women would access LIUS for HMB if the anaemia criteria were removed. Members noted that this is not a large patient group given the prevalence of HMB (about 10%; and 5% of women aged 30-49 years of age seeking medical advice), which suggests the current funding criteria are not being strictly followed.
  - 9.23. The Committee noted that widening access to LIUS for HMB would increase demand for access to trained inserters. The Committee considered that it would be clinically

acceptable to fund either a three-year or five-year LIUS, and that any Medsafe approved brand would be suitable. The Committee noted that training requirements would be the same regardless of brand.

## 10. Ocrelizumab for the treatment of relapsing remitting multiple sclerosis

### Application

- 10.1. The Committee reviewed the application for ocrelizumab in the treatment of relapse remitting multiple sclerosis.

### Recommendation

- 10.2. The Committee recommended the application for ocrelizumab in the treatment of relapse remitting multiple sclerosis be listed if it was cost neutral to other funded MS treatments.
- 10.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Information Reviewed

- 10.4. The application with all documentation provided by the applicant.
- 10.5. The following additional information:
  - [Minutes of November 2014 PTAC meeting relating to dimethyl fumarate for relapsing remitting multiple sclerosis and teriflunomide for multiple sclerosis](#)
  - [Minutes of February 2014 PTAC meeting relating to Neurological Subcommittee minutes September 2013](#)
  - [Minutes of February 2013 PTAC meeting relating to fingolimod in multiple sclerosis](#)
  - [Minutes of July 2012 Neurological Subcommittee meeting relating to for multiple sclerosis](#)
  - **Minutes of June 2012 MSTAC meeting**
  - [Minutes of May 2012 PTAC meeting relating to natalizumab for multiple sclerosis](#)
  - [Minutes of February 2012 PTAC meeting relating to multiple sclerosis](#)
  - [Minutes of May 2011 PTAC meeting relating to natalizumab for multiple sclerosis](#)
  - [Minutes of August 2010 PTAC meeting relating to natalizumab for multiple sclerosis](#)
  - [Buchanan et al. Int J MS Care 2011;13:76-83](#)
  - [Figved et al. J Neurol Neurosurg Psychiatry 2007;78:1097–1102](#)
  - [Hauser et al. New Engl J Med 2017;376:221-34](#)
  - [Kappos et al. Lancet; 2011;378:1779-87](#)
  - [Polman et al. N Engl Med 2006;354:899-910](#)
  - [Yhav et al. Mult Scler 2005;11:464-8](#)

### Discussion

- 10.6. The Committee noted that ocrelizumab is a humanised monoclonal antibody that selectively targets CD20, which is a cell-surface antigen that is expressed on pre-B cells, mature B cells and memory B cells. The Committee noted that humanised anti-CD20 antibody reduces immunogenicity compared to chimeric rituximab. The Committee noted that compared with rituximab, ocrelizumab recognises an overlapping but non-identical epitope. It is thought to have a greater binding affinity for CD20 than rituximab. Ocrelizumab exhibits higher (2- to 5-fold) antibody-dependant cell-mediated cytotoxicity. The Committee noted that by increasing antibody dependant cell mediated cytotoxic effects, ocrelizumab might modulate tissue-dependant mechanisms of pathogenic response more effectively than rituximab.

- 10.7. The Committee noted that ocrelizumab has not previously been considered by PTAC or the Neurological Subcommittee for relapsing remitting multiple sclerosis (RRMS). The Committee noted that there are currently seven disease modifying treatments that PTAC had previously considered and were now listed in the Pharmaceutical Schedule for treating RRMS.
- 10.8. The Committee considered the Kappos et al. (2011) phase 2 study of ocrelizumab in relapsing remitting multiple sclerosis (RRMS). The Committee noted that at week 24 there were large reductions in the number of gadolinium-enhancing lesions, compared to placebo, for both the 600 mcg and 2000 mcg treatment groups. The Committee considered that the most clinically relevant study outcomes are sustained change in Expanded Disability Status Scale (EDSS) score and annualised relapse rate. Other measures are surrogate markers.
- 10.9. The Committee considered the Hauser (2017) pivotal study (OPERA I and II) comparing ocrelizumab with interferon beta-1a in RRMS. The Committee noted that compared with the lower efficacy treatment interferon beta-1a, ocrelizumab demonstrated superior efficacy with a 46% reduction in annual relapse rate and a 40% reduction in 12 week confirmed clinical disability.
- 10.10. The Committee considered the results from the first year of the four-year open label extension to the Hauser (2017) study. The Committee noted that patients who were treated with ocrelizumab from the start of the studies showed a sustained benefit after three years total treatment. Patients who switched from interferon beta-1a to ocrelizumab experienced reductions in relapse rates and in MRI T1 and T2 lesions. The Committee noted that serious adverse events were more likely in the interferon beta-1a group and there had been no recorded opportunistic infections.
- 10.11. The Committee noted that the applicant positions ocrelizumab as having similar efficacy to natalizumab. The Committee noted that the Polman (2006) study reported a 42% reduction in risk of confirmed disability progression over two years with natalizumab.
- 10.12. The Committee noted that 50% of the general population will be John Cunningham Virus (JCV) positive by age 20. Natalizumab has a warning of increased risk of progressive multifocal leukoencephalopathy (PML) in JCV positive patients. The Committee noted that to date, there have been no reports of PML in patients treated with ocrelizumab, other than one carry-over case attributed to previous treatment with natalizumab, with over 13,000 patient years of safety data accumulated across both multiple sclerosis and rheumatoid arthritis studies. The Committee noted that the current Medsafe data sheet does not require JCV testing or MRI monitoring for PML.
- 10.13. The Committee considered that while there have not been any documented cases of PML with ocrelizumab, there is immaturity of data relating to the potential risk for PML in JCV positive patients. The Committee noted that a four-year clinical trial extension is underway, so more safety data is being accumulated.
- 10.14. The Committee considered a company-sponsored network meta-analysis indirect comparison, Wilson et al. (2017), supplied by the applicant. This analysis compared ocrelizumab treatment indirectly with dimethyl fumarate, fingolimod and natalizumab. The Committee noted this study indicated that ocrelizumab may be more effective than dimethyl fumarate and fingolimod, but similar to natalizumab in reducing annual relapse rates. There was no signal that ocrelizumab had a higher incidence of adverse events than the other treatments. Ocrelizumab had a higher discontinuation rate than natalizumab but lower discontinuation rates than dimethyl fumarate and fingolimod. The Committee noted that under the UK MS Guidelines, ocrelizumab would be placed in the category 2 (high efficacy) group.
- 10.15. The Committee noted that the evidence provided by the applicant consisted of two large randomised trials with some early open label extension data, but considered that there was still a lack of data around the sequencing of treatment with other agents and ocrelizumab. The Committee considered that the network meta-analysis, Wilson et al. (2017), only provided indirect evidence of relative efficacy compared to other

- RRMS treatments. The Committee considered that a direct randomised trial would be needed to confirm ocrelizumab's efficacy relative to natalizumab and fingolimod.
- 10.16. The Committee noted that the applicant considers ocrelizumab to be cost saving if patients switch from natalizumab or fingolimod. The Committee considered that the network meta-analysis was not robust enough to support this conclusion and a direct comparison randomised trial would be required.
- 10.17. The Committee noted the likely market dynamics if ocrelizumab was funded. They considered that 25-50% of patients using natalizumab could switch to ocrelizumab and 25-50% patients using fingolimod or dimethyl fumarate could switch to ocrelizumab. The Committee considered that there is a lack of data about the sequencing of treatment from other agents to ocrelizumab and therefore is a potential fiscal risk from adding another line of treatment. The Committee considered that there could be a number of possible treatment sequencing options for ocrelizumab, including use as an additional line of treatment or reserving use for patients who cannot use other agents because of adverse events or contraindications.
- 10.18. The Committee noted that rituximab has a similar mode of action to ocrelizumab and that there is growing evidence for its use in treating RRMS. Rituximab has been used for a number of indications for many years, so has more data available about its safety profile.
- 10.19. The Committee noted that in February 2018 ocrelizumab was approved for RRMS in Australia by the PBAC for listing on the Pharmaceutical Benefits Scheme.
- 10.20. The Committee requested that the Neurological Subcommittee and MSTAC be asked for their views on the risk of using ocrelizumab in JCV positive patients, and likely fiscal risks associated with adding an additional line of therapy.
- 10.21. The Committee requested that the Neurological Subcommittee and MSTAC be asked for their views on treatment sequencing options for ocrelizumab.

## 11. Ocrelizumab for the treatment of primary progressive multiple sclerosis

### Application

- 11.1. The Committee reviewed ocrelizumab for the treatment of primary progressive multiple sclerosis

### Recommendation

- 11.2. The Committee recommended that ocrelizumab for the treatment of primary progressive multiple sclerosis be **declined**.
- 11.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Information Reviewed

- 11.4. The application with all documentation provided by the applicant
- 11.5. The following additional information:
- [Abdelhak et al. Front Neurol 2017;8:234](#)
  - [Buchanan et al. Int J MS Care. 2011;13:76–83.](#)
  - [Figved et al. J Neurol Neurosurg Psych 2007;78:1097–1102](#)
  - [Filippini G. Evid Based Med. 2017;22:215-6](#)
  - [Hawker et al. Ann Neurol 2009;66:460-71](#)
  - [Hauser et al. N Engl J Med 2008;358:676-88](#)
  - [Montalban et al. N Engl J Med 2017;376:209-20.](#)
  - [Polman et al. Ann Neurol 2011;69:292–302](#)
  - [Yhav et al. Multiple Sclerosis 2005;11:464-468](#)

## Discussion

- 11.6. The Committee noted that primary progressive multiple sclerosis (PPMS) is characterised by insidious progression of disability over years with no remission and low MRI activity. It is generally considered less inflammatory and more neurodegenerative than relapse remitting multiple sclerosis (RRMS), which is thought to be why it responds less well to disease modifying therapies. The Committee noted that a recent review of PPMS, Abdelhak et al. (2017), suggested the inflammatory process is driven by autoreactive apoptosis-resistant EBV-infected B cells, which manifests itself clinically in genetically predisposed individuals only after a specific age threshold is exceeded.
- 11.7. The Committee considered that there is a high unmet health need for patients with PPMS, as there are currently no other treatments indicated for PPMS.
- 11.8. The Committee noted that ocrelizumab is a humanised monoclonal antibody that selectively targets CD20, a cell-surface antigen that is expressed on pre-B cells, mature B cells and memory B cells. The Committee noted that humanised anti-CD20 antibody reduces immunogenicity compared to chimeric rituximab. The Committee noted that compared with rituximab, ocrelizumab recognises an overlapping but non-identical epitope. It is thought to have a greater binding affinity for CD20 than rituximab. Ocrelizumab exhibits higher (2- to 5-fold) antibody-dependant cell-mediated cytotoxicity. The Committee noted that by increasing antibody dependant cell mediated cytotoxic effects, ocrelizumab might modulate tissue-dependant mechanisms of pathogenic response more effectively than rituximab.
- 11.9. The Committee considered the HERMES trial, Hauser et al. (2008), a phase II trial of rituximab in RRMS and the OLYMPUS trial, Hawker et al. (2009), a phase II/III trial of rituximab in PPMS. The Committee noted that the HERMES trial reported a 91% reduction in gadolinium (Gd) enhancing lesions, whereas the OLYMPUS trial failed to show a reduction in confirmed disease progression after 96 weeks. The Committee noted that subgroup analysis of the OLYMPUS trial reported that patients under 51 years of age and those with Gd enhancing lesions at baseline were more likely to benefit from treatment, suggesting a beneficial effect of B-cell depletion with rituximab in younger PPMS with inflammatory activity.
- 11.10. The Committee considered the ORATORIO study, Montalban et al. (2017), a placebo controlled double-blind, double dummy study of ocrelizumab 600 mg every 24 weeks for 120 weeks vs placebo, and noted it was designed for a young cohort of patients with PPMS. The Committee noted that at baseline, the mean age of patients was 45 years. The trial met its primary efficacy endpoint of the percentage of patients with confirmed disability progression persisting for 12 weeks or longer: 32.9 vs. 39.3% (hazard ratio 0.76; 95% CI 0.59–0.98);  $p = 0.03$ ; an absolute improvement of 6.4%. The Committee noted that the results also favoured ocrelizumab over placebo for the first 4 of 5 secondary endpoints tested in a hierarchical manner. Members noted that in the subgroup analysis, the efficacy of ocrelizumab in patients with and without Gd enhancing lesions on T1-weighted MRI at baseline was directionally consistent with the overall trial population, however the trial was not powered to show between-group differences among any subgroups.
- 11.11. The Committee noted that adverse events reported in the ORATORIO study were more common with ocrelizumab than placebo, and included infusion reactions, upper respiratory tract infections and oral herpes infections. There was an imbalance of neoplasms, which occurred in 2.3% of ocrelizumab treated patients, compared with 0.8% with placebo, but there was no clinically significant difference in the rates of serious adverse events and serious infections. Post-marketing surveillance is ongoing to assess the incidence and mortality of breast cancer and other malignancies, the outcomes of pregnancy and surveillance for pancreatitis, cholecystitis, serious and opportunistic infections, progressive multifocal leukoencephalopathy and hepatitis B virus reactivation. The Committee noted that long term safety of ocrelizumab in MS is unknown because of unavailable data. The Committee noted that ocrelizumab currently carries an FDA black box warning for hepatitis B reactivation.

- 11.12. The Committee considered the Filippini (2017) commentary on the ORATORIO study. The Committee noted that patients who had an initial onset of disability progression then withdrew from the study with no confirmatory EDSS assessments, were considered as having progressed (i.e. imputed events). The Committee noted that the placebo group had a higher rate of patient withdrawal compared with the ocrelizumab group (34% and 21% respectively) and this analysis with imputed events may have introduced bias in favour of the ocrelizumab. The treatment effect decreased when censoring was applied at withdrawal of these patients (OR 0.86 (95%CI 0.62 to 1.19)). The Committee considered that despite the investigators in the ORATORIO trial reporting that fewer patients progressed during 2 years of ocrelizumab treatment than placebo controls, the sensitivity analysis on unimputed data, which is commonly used as the standard primary data for disability progression end point, showed the fragility of this claim. The Committee considered that endpoints in the ORATORIO study achieved significance when hazard ratios were used, but the same data would not have achieved significance if odds ratios for endpoints at a particular time were used.
- 11.13. The Committee noted that ocrelizumab has not been studied in combination with other MS therapies. The Committee considered that the potential for increased immunosuppressive effects should be considered when initiating ocrelizumab after an immunosuppressive therapy or using it concomitantly with another immunosuppressive therapy. The Committee noted that the safety of immunisation with live or live attenuated vaccines following ocrelizumab has not yet been studied.
- 11.14. The Committee noted that the FDA has required the sponsor to conduct several Phase IV clinical trials, including: a two-part study in people aged between 10 and 17 years with relapsing multiple sclerosis to determine dosing, then safety and efficacy in these people, required to be completed by 2024; a prospective five-year study to better understand the risk of cancer, required to be completed by 2030; a prospective study creating a registry of women with MS exposed to ocrelizumab before and during pregnancy, women with MS not exposed to ocrelizumab, and women without MS, to understand the effect on women and children they might bear, due by 2029; and an additional pregnancy outcomes study, due by 2024.
- 11.15. The Committee considered that the evidence provided for this application consisted of a single, company sponsored, Phase III trial of low quality (downgraded for risks of bias and imprecision), which showed a modest reduction in the absolute risk of confirmed disability progression at 12 weeks of 6.4% compared to placebo, in possibly a select group of patients (younger with more MRI evidence of inflammation). The Committee noted this trial used an imputed design for withdrawals; and if this data is censored, the benefits are smaller.
- 11.16. The Committee considered that the long-term safety of ocrelizumab is unknown, and the effect of combined immune suppression with other disease modifying treatments is unknown.
- 11.17. The Committee considered, for purposes of assessing cost-effectiveness, it is unknown whether a PPMS patient in a given EDSS state differs in their quality of life from a RRMS patient in the same EDSS state. However, as the prognosis with PPMS is worse, there may be an increased risk of depression. The Committee considered that care should be taken in calculating dose duration and frequency (4 x 6 hours of infusions) of treatment.
- 11.18. Overall the Committee considered that despite the high unmet health need in patients with PPMS there were significant concerns with the application. There was a lack of data to establish both the safety and efficacy in this currently untreated group, and the pivotal study was perceived to have bias. The Committee noted that more studies were on-going, and likely to be reporting in the near future, which may address some of these concerns.

## 12. Secukinumab for the treatment of ankylosing spondylitis and psoriatic arthritis

### Application

- 12.1. The Committee reviewed the application for secukinumab in the treatment of ankylosing spondylitis and psoriatic arthritis

### Recommendation

- 12.2. The Committee **recommended** that the application for secukinumab in the treatment of ankylosing spondylitis arthritis as first biologic line (same criteria as adalimumab or etanercept) be deferred until the results of the SURPRASS trial are released.
- 12.3. The Committee **recommended** that the application for secukinumab in the treatment of ankylosing spondylitis arthritis as second biologic line (after failure of adalimumab or etanercept) be listed with a **medium priority**.
- 12.4. The Committee **recommended** that the application for secukinumab in the treatment of psoriatic arthritis as first biologic line (same criteria as adalimumab or etanercept) be listed with a **medium priority**.
- 12.5. The Committee **recommended** that the application for secukinumab in the treatment of psoriatic arthritis as second biologic line (after failure of adalimumab or etanercept) be listed with a **medium priority**.
- 12.6. The Committee **recommended** that the applications for secukinumab in the treatment of all above indications be referred to the Rheumatology Subcommittee for advice on dosing and patient numbers.

### Information Reviewed

- 12.7. The application with all documentation provided by the applicant
- 12.8. The following additional information:
- 12.9. [Mease et al. N Engl J Med 2015;373:1329-39](#)
- 12.10. [McInnes et al. Lancet 2015; 386: 1137-46](#)
- 12.11. [Baeten et al. N Engl J Med 2015;373:2534-48](#)
- 12.12. [Sieper et al. Ann Rheum Dis 2017;76:571-5](#)
- 12.13. [van der Heijde et al. Arthritis Rheum. 2006;54:2136–46](#)
- 12.14. [Strand et al. Rheumatol Ther. 2017;4:349-362](#)
- 12.15. [CADTH Canadian Drug Expert Committee Final Recommendation Cosentyx for Psoriatic Arthritis](#)
- 12.16. [Pharmaceutical Benefits Advisory Committee Minutes March 2016 regarding secukinumab.](#)

### Discussion

#### Secukinumab

- 12.17. Secukinumab is an IL-17A monoclonal antibody that is delivered by subcutaneous injection. It is registered with Medsafe for the treatment of adult patients with active psoriatic arthritis when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate, and for the treatment of adult patients with active ankylosing spondylitis. It is also indicated for moderate to severe plaque psoriasis, which PTAC discussed at its meeting of September 2017.

#### Ankylosing spondylitis (AS)

- 12.18. The Committee noted that the prevalence of AS in New Zealand is unknown but that internationally it is around 0.2-0.3% of the population. AS is strongly associated with the allele HLA-B27 which is less common in Māori.

- 12.19. The Committee considered that AS leads to significant loss of quality of life, with an EQ-5D score of 0.69 including disability and unemployment, uveitis, and inflammatory bowel disease.
- 12.20. The Committee noted that prior to funded biologics, treatment consists of NSAIDs and exercise. Failure of this regimen is high: around 50% of AS patients reach treatment with biologic agents, and that perhaps around 10-15% of AS patients do so and then do not gain control of AS symptoms despite using biologic agents. The Committee considered that patients with concomitant uveitis or inflammatory bowel disease respond well to TNF- $\alpha$  inhibitors.
- 12.21. The Committee considered that, if secukinumab is funded for AS, it would not simply replace existing biologics, but would instead increase the total time an average AS patient is on some biologic treatment. The Committee considered it could not comment on how long that extension would be due to a lack of data.
- 12.22. The Committee considered that the pivotal trials assessing secukinumab in AS are the MEASURE-1, MEASURE-2, and MEASURE-3 trials (Baeten et al *N Engl J Med* 2015; 373:2534-48 and Pavelka et al *Arthritis Research & Therapy* 2017; 19:285). These trials compared secukinumab at various doses against placebo in patients with AS, with the primary outcome measured at 24 weeks.
- 12.23. The Committee also reviewed two studies indirectly comparing secukinumab against adalimumab. The Committee noted that the makers of each agent had sponsored the study, and each study concluded that the sponsors' agent was preferable. The Committee considered that these studies were biased and could not be used to compare secukinumab against adalimumab. The Committee noted no indirect studies were found comparing secukinumab to other biologics.
- 12.24. The Committee considered that the placebo-controlled studies are of high quality and strength in demonstrating clear evidence of benefit against placebo. However, PTAC considered that there is poor quality evidence of secukinumab's benefit compared to currently available biologic agents.
- 12.25. The Committee considered that the trials collectively showed that there was not a significant difference between a 75 mg/month dose and a 150 mg/month dose, but that the loading dose appeared to play a large role in meeting the 24-week primary outcomes. The Committee discussed whether a 75 mg/month would be more cost-effective, though it was noted the smallest registered product was a 150 mg form. The Committee also discussed patients who would require the higher dose of 300 mg/month, noting that the Medsafe datasheet recommends a 300 mg/month dose for patients who received an inadequate response to TNF-alpha inhibitors.
- 12.26. The Committee considered the safety of secukinumab and considered that MEASURE-1 and MEASURE-2 showed higher infection rates in secukinumab treatment than in placebo, as well as higher rates of common adverse events such as nasopharyngitis and dyslipidaemia.
- 12.27. The Committee noted an upcoming trial of secukinumab in AS comparing against an adalimumab biosimilar (the SURPASS study) which has not yet begun recruitment.
- 12.28. The Committee noted that secukinumab is a subcutaneous injection which would have advantages over infusions such as infliximab. The Committee also noted that it was a monthly injection compared to fortnightly adalimumab or weekly etanercept, which would decrease discomfort from injections.
- 12.29. The Committee noted that the current criteria for renewing biologics in AS required an improvement in BASDAI score, specifically an improvement of 4 or more points on the 10-point scale or an improvement of 50%. The Committee noted that the average BASDAI score improvements shown in the MEASURE trials would not meet the current renewal criteria. The Committee considered that, should secukinumab be funded, PHARMAC may wish to consider this when determining secukinumab's renewal criteria.

- 12.30. The Committee considered that since the appropriate comparators for secukinumab were the other funded biologic agents, and since evidence against these biologic agents was very poor, the Committee could not recommend secukinumab for AS with the same restrictions as for other biologics at this time. Instead, the Committee deferred making a recommendation for secukinumab as a first biologic treatment of ankylosing spondylitis until the results of the SURPASS trial were available for consideration.
- 12.31. The Committee considered that evidence for secukinumab in the 2nd biologic line setting, in patients with ankylosing spondylitis where adalimumab or etanercept had failed, was sufficient to recommend funding with a medium priority, based on the evidence from the MEASURE-2 and MEASURE-3 trials as well as the health need of these patients and limited other therapeutic options.

### **Psoriatic arthritis (PsA)**

- 12.32. The Committee noted that psoriasis was a common skin disease, occurring in 3% of adults and under 1% of children, and PsA occurs in 15-25% of psoriasis sufferers.
- 12.33. The Committee considered that PsA causes significant disability, noting a study that reported an EQ-5D quality of life score of 0.67, and other studies showing PsA significantly inhibits usual activities such as ability to work.
- 12.34. The Committee noted that for 20-25% of PsA patients, non-biologic DMARDs including methotrexate and sulfasalazine will be inadequate, and most of those patients will meet the criteria for funding of a biologic. The Committee estimated that only 70% of patients who try biologics will have an adequate clinical response, and that some patients are resistant to all three funded TNF- $\alpha$  inhibitors.
- 12.35. The Committee considered that the key evidence for use of secukinumab in PsA came from the FUTURE-1 and FUTURE-2 trials (Mease et al N Engl J Med 2015;373:1329-39, and McInnes et al Lancet 2015;386:1137-46). These trials compared various doses of secukinumab against placebo with the primary endpoint, ACR20, measured at 24 weeks.
- 12.36. The Committee also reviewed six studies that used data from secukinumab trials to compare the agent against other biologic treatments (Strand et al, Rheumatol Ther 2017;4:349-362; Nash et al. ACR/ARHP Annual Meeting, Abstract 1738, Poster, 2016; Greenberg et al. ACR/ARHP Annual Meeting, Abstract 1245, Poster, 2016; Lopes et al, 6th Latin America ISPOR Conference, Abstract PMS22, Poster, 2017; Korotaeva, Sovremennaa Revmatologia 2016;10(4):57-63; Goeree et al, J Medical Economics 2017; DOI: 10.1080/13696998.2017.1384737). The Committee noted that studies sponsored by the supplier of secukinumab reported that secukinumab was superior, while the study sponsored by the supplier of adalimumab reported that adalimumab was superior. The Committee also noted one independent study which concluded that secukinumab was superior in some ways.
- 12.37. The Committee considered the safety of secukinumab and considered that infections were more common in treatment groups in the FUTURE-1 trial but not in the FUTURE-2 trial. The Committee also noted a US report (Ibler et al. 2017) stating no difference in infection rates when compared with other biologics being used to treat plaque psoriasis.
- 12.38. The Committee considered that the placebo-controlled studies were of high quality and strength in demonstrating clear evidence of benefit against placebo. However, PTAC considered that the comparison studies were indirect and contradictory, making assessment of relative efficacy difficult. PTAC considered that there is poor quality evidence of secukinumab's benefit compared to currently available biologic agents. The Committee considered there was sufficient evidence of secukinumab's relative efficacy in PsA to recommend it at first biologic line with the same restrictions as currently apply to the TNF-inhibitors. The Committee also recommended that, due to the different mode of action to TNF-inhibitors, secukinumab be funded at 2nd biologic line following failure of a TNF-inhibitor.

12.39. The Committee noted an upcoming trial was being organised (the EXCEED trial) which will compare secukinumab with adalimumab in patients with PsA. The Committee noted this was scheduled to be completed in March 2020.