

PTAC meeting held on 9 & 10 November 2017 (minutes for web publishing)

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

PTAC may:

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

1. Subcommittee Minutes	3
Gastrointestinal Subcommittee	3
Respiratory Subcommittee	4
Ophthalmology Subcommittee	5
2. Correspondence	5
Dapagliflozin	5
Pembrolizumab	5
Emtricitabine with tenofovir fumarate for pre-exposure prophylaxis (PrEP)	6
3. Tyrosine kinase inhibitors for the treatment of advanced soft tissue sarcomas	6
Pazopanib	7
Sunitinib	8
4. Rituximab subcutaneous for the treatment of Non Hodgkin Lymphoma	9
5. Trastuzumab emtansine for HER-2 positive metastatic breast cancer	10
6. Exenatide for the treatment of Diabetes Mellitus	12
7. Empagliflozin for the treatment of Diabetes Mellitus	15
8. Rituximab for the treatment of neuromyelitis optica spectrum disorder (NMOSD)	17
9. Multiple Sclerosis Treatments Widening Access	21
Widening access to include Clinically Isolated Syndrome	21
Definition of Significant Relapse	23
Amending the stopping criteria to EDSS 6.5 for all patients	24
Use of an additional scale to assess effectiveness of treatment	25
General discussion	27
10. Gaucher Disease Request for Funding Proposal	27
11. Taliglucerase alpha for the treatment of Type 1 Gaucher's disease	29

1. Subcommittee Minutes

Gastrointestinal Subcommittee

- 1.1. Regarding item 4.28, the Committee considered that the fiscal risk of widening access to tenofovir or entecavir for patients with non-decompensated cirrhotic hepatitis B to be low. Members considered there would be small patient numbers, as these patients are already on anti-viral treatments. The Committee supported the Subcommittee's recommendation to change the access criteria to viraemia instead of viral load.
- 1.2. Regarding item 5.5, levofloxacin for second line treatment of *Helicobacter pylori*, the Committee noted that the Anti-infective Subcommittee had been reluctant to make a recommendation due to them not understanding the information provided by the Gastrointestinal Subcommittee. PTAC asked to see the information requested by the Anti-infective Subcommittee before making its recommendation.
- 1.3. Regarding item 5.14, half-dose macrogol 3350 and electrolyte-free macrogol 3350, the Committee considered that a half-dose can be managed without the listing of a new formulation. The Committee considered that an electrolyte-free presentation would be useful for paediatric patients who cannot tolerate, due to palatability, the electrolyte presentation. The Committee supported the Subcommittee's high priority recommendation in this patient group.
- 1.4. Regarding item 5.15, Vitamin D Liquid, the Committee considered that it would not be necessary to limit treatment below a specific age as the term 'paediatric' would adequately describe the intended patient group and that age-cut-offs in children were arbitrary – children do not change their health status on their 18th birthdays – and did not allow for patients older than cut-offs still needing access clinically. The Committee **recommended** that the proposed Special Authority be reworded to 'paediatric patients who cannot swallow tablets or capsules' instead of 'patients less than 12 years old'. The Committee noted there was a fiscal risk of listing this product for any age group (i.e. including adults) with difficulties relating to swallowing, i.e. removing age group-related restrictions could permit widespread (and clinically less-necessary) overuse for older patients in rest home settings, when funded alternatives were sufficient and effective.
- 1.5. Regarding item 5.15, the Committee also requested PHARMAC note that its advice on limiting liquid formulations below specific ages (and that age-cut-offs can be arbitrary – noting that children do not abruptly change their health status on their 18th birthdays) would apply to all paediatric settings across all therapeutic groups (beyond simply vitamin D liquid or the Gastrointestinal group). The Committee requested PHARMAC ensure mechanisms for recording this wider advice and advising all therapeutic group managers and other staff and Subcommittees, as a specific PTAC policy-related action point.
- 1.6. Regarding item 5.20, Zinc Sulphate, the Committee requested that this minute be forwarded to the Tender Medical Evaluation Subcommittee of PTAC (TMESC) for its consideration of bids relating to Zinc Sulphate.
- 1.7. Regarding item 7, Adalimumab Resubmission for Ulcerative Colitis, the Committee considered that this was a large patient group and potentially high budget risk. The Committee requested to review the evidence in support of the Subcommittee's recommendation.

- 1.8. Regarding item 8, Vedolizumab for Ulcerative Colitis and Crohns disease, the Committee noted interests declared by members of the Subcommittee and the advice that was provided by the Gastrointestinal Subcommittee. The Committee noted that this application was submitted by a clinical group and that vedolizumab was neither registered nor sought for registration in New Zealand. The Committee noted that PHARMAC intends to invite Takeda (the supplier of vedolizumab) to submit an application for funding, and the Committee requested it review the evidence from the supplier when an application is made for funding and registration in New Zealand.
- 1.9. Regarding item 10, Oral Viscous Budesonide for the treatment of eosinophilic oesophagitis, the Committee considered that recommending its' funding for paediatric patients but not for adults would cause issues with continuity of treatment, given this is a chronic condition that does not abruptly cease on a patient's 18th birthday. The Committee noted the advice provided by the Gastrointestinal Subcommittee, but requested the Committee be able to review the evidence for the use of oral viscous budesonide in adults and children before providing its advice.
- 1.10. Regarding item 11, Macrogol correspondence and Clozapine Coroner's Report, the Committee supported the Subcommittee's recommendation for first line use in patients being treated with clozapine. Members noted that the macrogol price has reduced significantly since listing in 2007, when the reason for its original restriction had been based on financial risk at the time. The Committee supported the recommendation to remove the Special Authority on macrogol, however, it also considered that this may present a large financial risk and could therefore be reviewed by this Committee as needed (if targeting to patient groups at greatest need and/or gaining most benefit became necessary).
- 1.11. The Committee noted and accepted the remainder of the draft record of the Gastrointestinal Subcommittee meeting.

Respiratory Subcommittee

- 1.12. The Committee noted the complete draft record of the Respiratory Subcommittee meeting held on 04 August 2017. The Committee considered that as the minutes remained in draft form, it could only comment on the draft minute rather than accept it.
- 1.13. The Committee noted the Subcommittee's recommendation in paragraph 6.8, which related to changing the age restriction for dornase alfa from the under 5 years age and 5 & over criteria to under 7 years age and 7 & over criteria, and considered that this proposal should be progressed with a high priority.
- 1.14. The Committee noted the Subcommittee's recommendation in paragraph 6.21, which related to widening access to omalizumab for the treatment of severe asthma. The Committee requested it be able to review the omalizumab utilisation data one year after implementing these widened criteria.
- 1.15. The Committee noted the Subcommittee's recommendation in paragraph 7.39 and 7.40, which proposed additional access criteria for pirfenidone and for nintedanib (should it be listed). The Committee considered that the word 'both' should be inserted above the proposed criteria, to reflect PTAC's original intent that there should be no switching between the agents (unless due to intolerance) and that the two agents should not be used concurrently.
- 1.16. The Committee noted the Subcommittee's recommendation to widen access to pirfenidone to those patients with %FVC predicted >80% and to remove the

discontinuation criteria. The Committee **recommended** that this proposal be brought back to PTAC in future for review.

1.17. The Committee noted the remainder of the draft record of the meeting.

Ophthalmology Subcommittee

1.18. The Committee noted a section of the draft record of the Ophthalmology Subcommittee held on 20 September 2017, relating to anti-VEGF agents for the treatment of wet age-related macular degeneration (wAMD) and diabetic macular oedema (DMO).

1.19. The Committee noted the restrictions proposed by the Ophthalmology Subcommittee and considered that the restrictions were appropriate for targeting treatment to patients who would most likely benefit. The Committee noted that the proposed exit criteria would limit the fiscal risk associated with 2nd line anti-VEGF agents.

1.20. The Committee noted paragraph 7.14 of the draft minute, and did not agree that the Subcommittee's view that Named Patient Pharmaceutical Assessment (NPPA) pathway would be the appropriate mechanism to assess patients who wished to go back to being treated with ranibizumab after switching to aflibercept due to intolerance.

1.21. The Committee considered that clinicians would have their own preferences and would exercise professional judgement as to which agent would work best for their patients when selecting treatment options.

1.22. The Committee considered that if aflibercept were also to be listed 2nd line alongside ranibizumab, that PHARMAC staff should include a time limited restriction to both ranibizumab and aflibercept so that patients who are currently using ranibizumab would be able to switch to being treated with aflibercept; after this time-limited period patients could switch treatments (i.e. aflibercept to ranibizumab, or ranibizumab to aflibercept) if intolerant.

1.23. The Committee noted its previous recommendation to decline a 3rd line anti-VEGF agent, and considered that the restriction should not allow switching between the agents if not due to intolerance.

2. Correspondence

Dapagliflozin

2.1. The Committee noted the correspondence to PHARMAC regarding dapagliflozin from Astra Zeneca Limited. The Committee noted that this had been submitted in relation to the agenda item for empagliflozin and additional information regarding the cardiovascular and/or renal related outcomes for type 2 diabetes patients.

2.2. The Committee noted that in essence the supplier was asking that the reported survival benefit for empagliflozin should be considered a class effect for the sodium-glucose co-transporter-2 (SGLT-2) inhibitor agents.

2.3. The Committee noted a large scale cardiovascular outcomes trial with dapagliflozin, the DECLARE trial, was under way and did not consider that at this time it should consider a change in its current low priority recommendation for this medication until the published results had been considered by PTAC.

Pembrolizumab

2.4. The Committee noted further information from the supplier of pembrolizumab, Merck Sharpe & Dohme, submitted in response to the May 2017 PTAC minutes regarding its

use as a first-line treatment of patients with previously untreated advanced non-small cell lung cancer whose tumours express PD-L1 at a level of greater than or equal to 50%.

- 2.5. The Committee noted that the supplier described ad hoc analysis in relation to an ASCO August 2017 meeting for overall survival and provision of a draft paper about longer-term overall survival from the KEYNOTE-024 trial.
- 2.6. The Committee indicated a preference for its advice to be based on the peer-reviewed pre-specified database-lock-related analysis in terms of magnitude and confidence intervals for estimates of survival differences. The Committee noted its advice regarding the use of pembrolizumab in this setting could also be better refined with publication of associated quality of life analyses.
- 2.7. The Committee noted correspondence from two New Zealand pathologists regarding PD-L1 testing.

Emtricitabine with tenofovir fumarate for pre-exposure prophylaxis (PrEP)

- 2.8. The Committee received a verbal update on an application to widen access to emtricitabine with tenofovir fumarate for pre-exposure prophylaxis (PrEP).
- 2.9. The update noted that the Anti-infective Subcommittee of PTAC reviewed the application at its meeting held last Thursday 2 November 2017.
- 2.10. The Committee noted that the Anti-infective Subcommittee recommended funding with a high priority for individuals who are at a high risk of contracting HIV.
- 2.11. The Committee noted there are two generics entering the New Zealand market shortly. PHARMAC is planning to consult on a proposal to widen access to emtricitabine with tenofovir fumarate for PrEP for high risk individuals, with the release scheduled for the week commencing 13 November 2017.

3. Tyrosine kinase inhibitors for the treatment of advanced soft tissue sarcomas

Application

- 3.1. The Committee considered a clinician funding application for the use of pazopanib for the treatment of advanced (unresectable and/or metastatic) soft tissue sarcoma (STS) in patients who, unless otherwise contraindicated, have received prior chemotherapy including anthracycline treatment.
- 3.2. The Committee noted that advice was also sought by PHARMAC staff regarding the funding of sunitinib for the treatment of advanced STS.

Recommendation

- 3.3. The Committee **recommended** that the application for pazopanib for the treatment of advanced STS in patients who, unless otherwise contraindicated, have received prior chemotherapy including anthracycline treatment be declined.
- 3.4. The Committee **recommended** that funding for sunitinib for the treatment of advanced STS be declined.

Discussion

- 3.5. The Committee noted that STS represent a spectrum of over 80 subtypes of tumours characterised by malignant growth of mesenchymal tissue. The Committee noted that different subgroups are divided based on genetics, pathology, anatomical location and clinical behaviour.

- 3.6. The Committee noted that STS are a heterogeneous group of malignancies that account for 1% of all adult cancers and 12% of all paediatric cancers; different histological subtypes occur more commonly in children compared to adults. The Committee noted that approximately 25% of STS patients will develop distant metastatic disease after successful treatment of their primary tumour; and for intermediate or high grade tumours around half metastasise and require systemic treatment.
- 3.7. The Committee noted that the majority of patients who develop advanced STS are incurable. The Committee had not reviewed any published national or international consensus statements regarding sarcoma treatment, other than that UK Sarcoma guidelines (Dangoor A et al. Clin Sarcoma Res 2016;6:20) which recommend treatment should partially be guided by potential sensitivity to treatment.
- 3.8. The Committee noted that funded treatment in New Zealand is primarily surgery and/or radiotherapy, with tyrosine kinase inhibitor (TKI) chemotherapy for gastrointestinal stromal tumours (GIST) or anthracycline for non-GIST. The Committee noted that second-line treatment options for relapsed advanced STS include docetaxel/gemcitabine or irinotecan/temozolomide combinations.
- 3.9. The Committee noted that 5 year overall survival for STS patients is around 55% but this decreases to around 18% if distant spread has occurred (Dangoor A et al. Clin Sarcoma Res 2016;6:20; NCIN Bone and soft tissue sarcomas. UK incidence and survival. 1996–2010. 2nd edn; 2013. p. 1–17).
- 3.10. The Committee noted that at its meeting in March 2017, the Cancer Treatments Subcommittee (CaTSoP) had considered a noting paper from PHARMAC staff regarding the use of sunitinib and pazopanib for the treatment of STS in the light of a number of recent NPPA applications for the use of TKIs in this patient group.
- 3.11. The Committee noted that CaTSoP had considered that the currently available evidence indicated that there were likely differences in the spectrum of activity of TKIs with different STS subtypes, but noted that this was based on studies of very small patient numbers and there were no comparative studies of TKIs with standard chemotherapy treatments. PTAC noted that CaTSoP members considered that from the currently available evidence some subtypes appear to have significant response rates to TKIs, but from the larger studies it is difficult to identify specific STS subtypes which are likely to derive clear benefit from treatment with TKIs.

Pazopanib

- 3.12. The Committee noted that subsequent to CaTSoP's advice, a clinician funding application had been received for the use of pazopanib for the treatment of advanced (unresectable and/or metastatic) STS in patients who, unless otherwise contraindicated, have received prior chemotherapy including anthracycline treatment.
- 3.13. The Committee noted that primary evidence for the use of pazopanib in advanced STS is from the PALETTE trial - a randomized, double-blinded, placebo-controlled phase III study of 369 adult patients with a variety of advanced STS histologic subtypes (leiomyosarcoma, fibrosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumour, vascular STS, sarcoma not otherwise specified) (Van der Graaf et al. Lancet 2012;379:1879–86; Kasper et al. Annals of Oncology 2014;25:719-24; Coens et al. Cancer 2015;121:2933-41).

- 3.14. The Committee noted that median progression-free survival, the primary end-point, was 4.6 months (95% CI 3.7–4.8) for pazopanib compared with 1.6 months (0.9–1.8) for placebo (hazard ratio [HR] 0.31, 95% CI 0.24–0.40; $p < 0.0001$) and overall survival was 12.5 months (10.6–14.8) with pazopanib versus 10.7 months (8.7–12.8) with placebo (HR 0.86, 0.67–1.11; $p = 0.25$), a 1.8 month difference in the point estimates of median survival in the two groups.
- 3.15. The Committee considered that analysis by histological subtype did not show a statistically different progression-free survival rate and that rare STS subtypes, such as desmoplastic small round cell tumour, also benefit from pazopanib.
- 3.16. The Committee noted that about one third of patients stopped treatment due to adverse events and 50% had a dose reduction. The Committee considered that it did not appear pazopanib improved quality of life at 12 weeks, but that individual quality of life components such as diarrhoea, loss of appetite, nausea or vomiting, and fatigue were significantly worse with pazopanib. The Committee considered that pazopanib appeared to be poorly tolerated without providing a quality of life benefit as improvement in patients' activity or wellbeing was not definitively shown.
- 3.17. The Committee noted evidence for the use of pazopanib in advanced STS from:
- Sleijfer et al. *J Clin Oncol* 2009;27:3126-32
 - Yoo et al. *BMC Cancer* 2015;15:154
 - Kawai et al. *Adv Ther.* 2017;34:1556-71
- 3.18. The Committee considered that there did not appear to be any trial evidence for the use of pazopanib in the treatment of paediatric advanced STS, but as the total numbers would be very low, considered it unlikely that trial evidence would eventuate.
- 3.19. The Committee considered that there were significant concerns regarding the quality of evidence to support the use of pazopanib in advanced STS; the evidence was adversely affected by the variety of tumour types included in the study populations.
- 3.20. The Committee considered that the currently published evidence indicated some advanced STS patients achieve benefit from treatment with pazopanib. However, there was uncertainty regarding survival benefit and quality of life due to the inclusion of only small numbers of each subtype. The Committee considered, based on current evidence, it was not possible to clinically differentiate those patients who would gain higher levels of benefit prior to commencing treatment.
- 3.21. The Committee also noted that the cost of TKI treatment was relatively low and the patient population was relatively small, however, pazopanib was associated with a reasonable level of adverse events which would incur a cost for their management.
- 3.22. The Committee considered that it was unclear whether there was a long-term benefit from pazopanib treatment as only a handful of patients from PALETTE remained alive, although noted that there was potential for some patients to be long-term survivors.
- 3.23. The Committee noted that generally funding was considered for a single tumour type but, due to the heterogeneity of STS, there were unlikely to be high-quality randomised controlled trials undertaken. However, the Committee recognised that there may be additional evidence published in future to support a differential benefit in specific STS subtypes and considered that this should be brought back for consideration once available.

Sunitinib

3.24. The Committee noted evidence for the use sunitinib in advanced STS from:

- George et al. J Clin Oncol 2009;27:3154-60
- Stacchiotti S, et al. Clin Cancer Res 2009;15:1096-104
- Stacchiotti S, et al. Ann Oncol 2010;21:1130-1
- Mahmood et al. Int J Cancer. 2011;129:1963-9
- Stacchiotti et al. Ann Oncol 2011;22:1682-90
- Stacchiotti et al. Clin Sarcoma Res 2012;2:22
- Italiano et al. Target Oncol 2013;8:211-3

3.25. The Committee considered that the evidence for the use of sunitinib in the treatments for STS is limited to case series and a phase 2 study only and there was significant uncertainty regarding its use in this patient population. Members considered that there appeared to be some level of activity in some STS subtypes.

4. Rituximab subcutaneous for the treatment of Non Hodgkin Lymphoma

Application

4.1. The Committee considered a resubmission from Roche Products (New Zealand) Limited (Roche) for subcutaneous rituximab for the treatment of non-Hodgkin lymphoma that had previously been recommended for decline by PTAC in February 2016.

Recommendation

4.2. The Committee **recommended** that the reapplication from Roche for subcutaneous rituximab for the treatment of non-Hodgkin lymphoma be declined.

Discussion

4.3. The Committee noted the minutes from their previous consideration of subcutaneous rituximab in February 2016. The Committee, at that meeting, had concerns about the comparative efficacy and the potential effect of listing the subcutaneous preparation on future biosimilar competition, but agreed that there were potential advantages to subcutaneous administration compared to a time-consuming intravenous infusion.

4.4. The Committee noted Roche's August 2017 submission that included updated and now published clinical data from the SABRINA study, a new time and motion study, and a modified commercial proposal that reflects the rituximab price reduction that occurred in 2016.

4.5. The Committee noted that the 1400 mg presentation of subcutaneous rituximab is indicated for the treatment of patients with non-Hodgkin lymphoma (NHL), and a 1600 mg presentation is also indicated for chronic lymphocytic leukaemia (CLL). The Committee noted that although maintenance treatment was a registered indication, it is not currently funded in this setting.

4.6. The Committee noted that each patient must receive their first dose of rituximab by intravenous infusion due to the risk of infusion reactions. Members discussed the current management of these intravenous infusion reactions which usually involves temporary discontinuation or slowing of the infusion and providing supportive care measures, rather than ceasing the infusion altogether. The Committee considered the risk of unexpected reactions following subcutaneous rituximab in patients who did not experience any problems with the intravenous dose was low, due to the slow rate of release from the tissue site.

- 4.7. The Committee noted the subcutaneous administration of rituximab requires delivery of a volume (11.7 ml) that would be considered unusual for a medication administered via the subcutaneous route.
- 4.8. The Committee noted the MabCute trial which will provide further clinical outcome evidence for subcutaneous rituximab in the maintenance setting. This study is due for completion in late-2018. The Committee noted that the subcutaneous rituximab formulation may be more relevant and potentially useful in the setting of long-term maintenance when no other concurrent chemotherapy is required
- 4.9. The Committee noted the updated SABRINA Stage II data, which was provided for the previous PTAC consideration, has now been published ([Davies et al. Lancet Haematol. 2017;4:e272–82](#)). The Committee noted this study was only powered sufficiently to detect pharmacokinetic non-inferiority, despite collecting efficacy and adverse event data. The Committee therefore broadly disagreed with the interpretation of the authors that this study demonstrated that the intravenous and subcutaneous presentation of rituximab have similar clinical efficacy and safety profiles.
- 4.10. The Committee also noted a new time in motion study ([De Cock et al. PLoS One. 2016;11:e0157957](#)). The Committee noted that the study reported savings in health professional and patient chair-time, however it demonstrated substantial variations in practice. The Committee noted that reduced administration time was likely of some benefit to patients, their families, and health services, although noted the significant inter-country variation, particularly in the infusion times for intravenous rituximab, made comparisons difficult. The Committee noted the supplier has suggested data from Brazil closely reflect the clinical routine in New Zealand, but it remained unclear whether this was truly applicable to the New Zealand setting.
- 4.11. The Committee noted the PrefMab patient preference study ([Rummel et al. Ann Oncol. 2017;28:836-42](#)). The Committee noted that, during 8 cycles of treatment, the main reasons for the patient preference for subcutaneous rituximab were less clinic hospital chair time, more comfortable administration, and less emotional distress.
- 4.12. The Committee considered that overall the clinical benefit of fixed-dose subcutaneous rituximab over the intravenous administration based on body surface area remained unproven. The Committee thus did not support its listing until there was additional robust clinical evidence to support an equivalent outcome in terms of efficacy in at least one indication.

5. Trastuzumab emtansine for HER-2 positive metastatic breast cancer

Application

- 5.1. The Subcommittee considered a funding application from Roche NZ Ltd for trastuzumab emtansine for the second-line treatment of patients with HER-2 positive metastatic breast cancer who have previously received trastuzumab and a taxane, separately or in combination.

Recommendation

- 5.2. The Subcommittee **recommended** that trastuzumab emtansine be funded with low priority for second-line treatment of patients with HER-2 positive metastatic breast cancer who have previously received trastuzumab and a taxane.
- 5.3. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee for advice regarding the likely benefit for patients previously treated with pertuzumab, impact on quality of life, appropriate place and sequence in

New Zealand treatment settings, estimated patient numbers, and proposed access criteria.

Discussion

- 5.4. The Committee noted that breast cancer is the most commonly diagnosed cancer for women with 3,025 new cases of breast cancer registered in 2012. The Committee noted that approximately 10% of women present with metastatic disease at the time of diagnosis, however, the majority of patients who relapse after definitive therapy will do so with disseminated metastatic disease.
- 5.5. The Committee noted that Māori women have higher incidence rates of breast cancer and higher breast cancer mortality rates, with differences attributed largely to later presentation of disease and less favourable biology.
- 5.6. The Committee noted that HER-2 is overexpressed in 15%-20% of breast cancers, and considered that it was reasonable to expect around 100 patients with HER-2 positive metastatic breast cancer (mBC) per year who may seek a second-line treatment. The Committee considered that there would likely be a high rate of uptake, given the established use of trastuzumab emtansine internationally.
- 5.7. The Committee noted that funding applications for trastuzumab, lapatinib, pertuzumab and nab-paclitaxel as second-line mBC treatments have been previously considered by PTAC and CaTSoP.
- 5.8. The Committee noted that trastuzumab emtansine is a HER2-targeted antibody-drug conjugate that contains trastuzumab linked to microtubule inhibitory DM1 (together referred to as TDM1). The Committee noted that the mechanism of action includes trastuzumab binding of the HER-2 receptor, internalisation, and degradation which releases DM1 leading to cell death.
- 5.9. The Committee noted that the primary evidence for the use of trastuzumab emtansine for the treatment of HER-2 positive mBC was from two open-label, phase 3 studies: TH3RESA and EMILIA; and three phase 2 studies TDM4374g, TDM4258g, and JO22997.
- 5.10. The Committee noted that the TH3RESA study (Krop et al. Lancet Oncol 2017;18:743-54) was a study of trastuzumab emtansine (n=404) vs treatment of physicians choice (including chemotherapy, HER-2 directed therapy, and hormonal therapy, n=198) in patients with HER2-positive advanced breast cancer previously treated with both trastuzumab and lapatinib (advanced setting) and a taxane (any setting) and with progression on two or more HER2-directed regimens in the advanced setting.
- 5.11. The Committee noted that the EMILIA study (Dieras et al Lancet Oncol 2017;18:732-42) was a study of trastuzumab emtansine (n=495) vs. capecitabine plus lapatinib (n=496) in patients with HER-2 positive unresectable, locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.
- 5.12. The Committee noted that it was unclear why around 10% of screened patients in both the TH3RESA and EMILIA studies were excluded, as the reason for exclusion was not specified, and considered that given the population size this may be significant. The Committee also considered there were high rates of crossover to other treatment in both studies.
- 5.13. The Committee noted that at a median follow-up of 41.9 months (interquartile range (IQR) 34.6-50.7) in the control group and 47.8 months (IQR 41.9-55.5) in the trastuzumab emtansine group, median overall survival (OS) in the intention-to-treat

EMILIA study population was 25.9 months (95% CI 22.7–28.3) in the control group vs. 29.9 months (95% CI 26.3–34.1) in the trastuzumab emtansine group (hazard ratio 0.75, 95% CI 0.64–0.88). The Committee noted that lapatinib was not an appropriate comparator treatment as it is not currently funded for use in a second-line setting in New Zealand. The Committee considered that, based on an indirect comparison to capecitabine monotherapy, the appropriate comparator, there appeared to be an OS gain of around 12 months from the use of trastuzumab emtansine in the EMILIA trial population.

- 5.14. The Committee noted that the supplier had proposed trastuzumab emtansine as a second-line treatment option in the New Zealand setting. The Committee considered that the majority of these patients would have received pertuzumab in combination with trastuzumab as a first-line treatment. The Committee considered that there was a lack of published studies where patients were sequentially treated with pertuzumab prior to trastuzumab emtansine, and considered the evidence for this group was sourced from only a very limited number of patients.
- 5.15. The Committee noted it appeared the only publication including sequentially treated patients was a retrospective two centre study of 82 patients (Dzimitrowicz et al JCO 2016;34;3511-7) in which 32% of patients were treated with TDM1 as first and second-line, and 48% were fourth-line or later. The Committee noted that median duration of treatment was 4 months and, by extrapolation, it appeared that around 30% of patients were on TDM1 for greater than 6 months.
- 5.16. The Committee considered that with the available evidence there was uncertainty regarding the benefit patients previously treated with pertuzumab would receive from trastuzumab emtansine. The Committee considered that the general trend with oncology treatments was for reduced efficacy when used as later line treatment. The Committee considered that it was unlikely the evidence base for sequentially treated patients would improve substantially in future, given international treatment paradigms for mBC.
- 5.17. The Committee noted that very few of the publications in the application regarding reduced quality of life for patients with mBC were relevant to the population under consideration; and that published quality of life data from the EMILIA study had not been included. The Committee noted the applicant had highlighted that mBC patients have diminished quality of life due to pain, fatigue and anxiety, but the Committee considered that from published data it was difficult to interpret whether the effect of the new treatment was clinically or statistically significant.
- 5.18. Overall, the Committee considered that there was reasonable evidence, although only from open-label studies, of some survival benefit in those patients previously treated with trastuzumab in the first-line setting. However, the Committee noted there was little evidence that supported its use in a pertuzumab/trastuzumab pre-treated mBC population. The Committee considered that at the pricing sought by the supplier trastuzumab emtansine was expensive in relation to the uncertainties about its benefit in the requested clinical population.
- 5.19. The Committee considered that the general standard of the supplier's application was poor, particularly with regards to the inclusion of very large amounts of information of unclear relevance and considered that relevant information, in particular quality of life material, was missing from the application.

6. Exenatide for the treatment of Diabetes Mellitus

Application

- 6.1. The Committee considered an application from a supplier for exenatide as a once weekly formulation (Bydureon) for the treatment of patients with type 2 diabetes mellitus.
- 6.2. The Committee noted that advice was also sought by PHARMAC staff regarding whether exenatide once weekly has a similar clinical effect to other GLP-1s or other diabetic agents.

Recommendation

- 6.3. The Committee **recommended** that exenatide once weekly be funded with a low priority for patients with type 2 diabetes.
- 6.4. The Committee **recommended** that application be referred to the Diabetes Subcommittee for advice regarding appropriate access criteria for antidiabetic agents.

Discussion

- 6.5. The Committee noted that the health need of patients with type 2 diabetes has been well-documented in previous PTAC and subcommittee minutes during consideration of various antidiabetic agents, in particular the significant burden that type 2 diabetes places on Pacific peoples, Māori and South Asian populations which have more prevalent, more severe, and generally earlier onset of disease.
- 6.6. The Committee noted that applications for antidiabetic agents have been reviewed by PTAC and the Diabetes Subcommittee individually and together on a number of occasions. The Committee noted that PTAC had previously recommended that these agents were generally similar in the treatment of type 2 diabetes in terms of reducing HbA1c by approximately 0.5%-1% and that there was a lack of evidence supporting other clinically significant long-term benefits. The Committee noted that its previous recommendations were for funding each agent with a low priority. The Committee noted that none of these agents were currently funded in New Zealand.
- 6.7. The Committee noted that at its meeting in February 2017 PTAC had noted there was new published evidence for some of these agents, in particular empagliflozin and liraglutide, which reported additional health benefits including reductions in renal complications, death from cardiovascular causes, and all-cause mortality. The Committee noted that it had requested to re-review these two individual agents, and that part of the review should include consideration of class effects.
- 6.8. The Committee noted that additional information regarding empagliflozin had been provided, as had additional information regarding exenatide. The Committee reiterated that funding for liraglutide should be re-reviewed in light of updated evidence.
- 6.9. The Committee noted that exenatide BD, a twice daily formulation (Byetta), had previously been reviewed and was recommended for decline by PTAC in 2007 and 2008, due to limited additional benefit over insulin and a high cost. The Committee noted that this was revised to low priority in 2012 when all glucagon-like peptide-1 (GLP-1) agonists were recommended for funding for patients with a BMI > 35 kg/m².
- 6.10. The Committee noted exenatide once weekly (OW) is a subcutaneous injectable extended-release GLP-1 receptor agonist formulation developed as an extension to exenatide twice daily injection product line for the treatment of type 2 diabetes mellitus. Members noted that exenatide OW is a prolonged release formulation of exenatide but considered that there appeared to be no other differences in the pharmacological mechanism of action.

- 6.11. The Committee considered evidence to support the use of exenatide OW for the treatment of type 2 diabetes, including the following:
- DURATION-1 (Drucker et al. Lancet 2008;372:1240-50, Buse et al. Diabetes Care. 2010;33:1255-61, Chiquette et al. Vascular Health and Risk Management 2012;8:621-9)
 - DURATION-2 (Bergenstal et al. Lancet 2010;376:431-9)
 - DURATION-3 (Diamant et al. Lancet. 2010;375:2234-43, Diamant et al. Diabetes Care. 2012;35:683-9, Diamant et al. Lancet Diabetes Endocrinol 2014 2:464-73)
 - DURATION-4 (Russell-Jones et al. Diabetes Care. 2012;35:252-8)
 - DURATION-5 (Blevins et al. J Clin Endocrinol Metab 2011;96:1301-10)
 - DURATION-6 (Buse et al. Lancet. 2013;381:117-24)
 - DURATION-8 (Frias et al. Lancet. 2016;4:1004-16)
 - GWBX (Inagaki et al. Clinical Therapeutics. 2012;34:1892-908)
 - GWCL (Ji et al. J Diabetes Invest. 2013;4:53-61)
 - GWDC (Norwood et al. Clinical Therapeutics. 2012;34:2082-90)
 - GWDL (Davies et al. Diabetes Care. 2013;36:1368-76)
 - EXSCEL (Holman et al. NEJM. 2017; DOI: 10.1056/NEJMoa1612917)
- 6.12. The Committee considered that there were a large variety of studies with varying patient population characteristics. The Committee considered that, from the currently available evidence, there is uncertainty regarding the level of benefit exenatide OW provides for patients with type 2 diabetes, other than the reduction in HbA1c.
- 6.13. The Committee noted that the EXSCEL trial was intended to demonstrate clinical improvement in a composite primary outcome of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, however the trial failed to show statistical superiority versus placebo ($p=0.06$).
- 6.14. The Committee considered that there was a lack of robust quality of life data for exenatide OW in the published literature. The available evidence suggests that the OW formulation is no better than the BD formulation.
- 6.15. Overall, the Committee considered that the benefit of exenatide OW to be comparable to that of exenatide BD, in that it reduces HbA1c by around 0.7%-1% which is of a similar order of to all of the previously considered anti-diabetic agents.
- 6.16. The Committee considered that the estimates in the EXSCEL trial of the effects on cardiovascular outcomes from exenatide OW were consistent with a benefit, however, the confidence intervals in that study were wide and consistent with no effect. The Committee considered that this may be consistent with a class effect for GLP-1 agonists.
- 6.17. The Committee noted that the supplier had indicated outcomes from EXSCEL should be compared to the LEADER and SUSTAIN-6 trials for sodium-glucose co-transporter 2 (SGLT-2) agents. The Committee considered that, as the baseline characteristics of these trials were different, comparison between them was difficult.
- 6.18. The Committee considered it was possible that use of a OW formulation may be helpful in terms of improved adherence to treatment when compared to alternatives that require multiple doses per day, although the published data to support this showed only a weak benefit. The Committee considered that there was no data to support improved outcomes as a result of improved adherence with exenatide OW.

- 6.19. The Committee considered that the additional evidence regarding exenatide was insufficient to increase the Committee's low priority recommendation. The Committee requested that in the future, any further published evidence to support the use of exenatide should be presented to PTAC for review.
- 6.20. The Committee considered that exenatide would likely be taken alongside standard diabetes treatments currently available in New Zealand such as insulin and metformin; and should more than one antidiabetic agent be funded these would also be used in combination as is the practice internationally. Members considered that it was possible that exenatide may delay the commencement of insulin, however it would not prevent eventual progression to the use of insulin. The Committee considered that use of exenatide, particularly as part of combination therapy, would represent a significant fiscal impact.
- 6.21. The Committee considered that were exenatide OW, or any other antidiabetic agent, funded in New Zealand, there would be a high level of uptake in all eligible type 2 diabetic patients.

7. Empagliflozin for the treatment of Diabetes Mellitus

Application

- 7.1. The Committee considered an application from a supplier for the use of empagliflozin for the treatment of patients with type 2 diabetes with high cardiovascular risk.

Recommendation

- 7.2. The Committee **recommended** that empagliflozin for the treatment of patients with type 2 diabetes with established high cardiovascular risk be funded with a high priority, noting the importance of appropriately defining this population.
- 7.3. The Committee **recommended** that the application be referred to the Diabetes Subcommittee for advice regarding appropriate access criteria, including definition of a high cardiovascular risk population.

Discussion

- 7.4. The Committee noted that the health need of patients with type 2 diabetes has been well-documented in previous PTAC and subcommittee minutes during consideration of various antidiabetic agents, in particular the significant burden that type 2 diabetes places on Pacific people, Māori and South Asian populations which have more prevalent, more severe, and generally earlier onset of disease.
- 7.5. The Committee noted that applications for antidiabetic agents have been reviewed by PTAC and the Diabetes Subcommittee individually and together on a number of occasions. The Committee noted that PTAC had previously recommended that these agents were generally similar in the treatment of type 2 diabetes in terms of reducing HbA1c by approximately 0.5% to 1% and that there was a lack of evidence supporting clinically significant long-term benefits other than decreased HbA1c. The Committee noted that its previous recommendations were for funding each agent with a low priority. The Committee noted that none of these agents were currently funded in New Zealand.
- 7.6. The Committee noted that at its meeting in February 2017 PTAC had noted there was new published evidence for some of these agents, in particular empagliflozin and liraglutide, which reported health benefits in addition to improving glycaemic control, particularly reductions in renal complications, death from cardiovascular causes, and all-cause mortality. The Committee noted that it had requested to re-review these

- individual agents, and that part of the review should include consideration of class effects.
- 7.7. The Committee noted that additional information regarding empagliflozin had been provided, as had additional information regarding exenatide. The Committee reiterated that funding for liraglutide should be re-reviewed in light of updated evidence.
- 7.8. The Committee noted that empagliflozin is a reversible competitive inhibitor of sodium-glucose co-transporter 2 (SGLT-2) which had previously been considered by PTAC and recommended for funding with low priority for patients with type 2 diabetes.
- 7.9. The Committee noted that the supplier had provided additional evidence for the use of empagliflozin and proposed its use as second or third line adjunct therapy, along with other measures to reduce cardiovascular risk in line with the current standard of care, for type 2 diabetes patients with high cardiovascular risk who remain above target HbA1c.
- 7.10. The Committee noted that empagliflozin would be used in addition to insulin.
- 7.11. The Committee considered evidence to support the use of empagliflozin for the treatment of type 2 diabetes with high cardiovascular risk to reduce the risk of cardiovascular death, including the following:
- Trial 1245.10 (Rosenstock et al Diabetes Obes Metab. 2013;15:1154-60)
 - Trial 1245.23 (Håring et al Diabetes Care 2014;37:1650-9) and its extension, Trial 1245.31 (Merker et al. Diabet Med. 2015;32:1555-67)
 - Trial 1245.25 (Zinman et al N Engl J Med 2015;373:2117-28) and trial 1245.26 (Wanner et al N Engl J Med 2016;375:323-34), which make up the EMPA-REG OUTCOME study
 - Trial 1245.28 (Ridderstråle et al Lancet Diabetes Endocrinol. 2014;2:691-700)
 - The Zhong et al meta-analysis Eur J Clin Pharmacol 2016;72:655-63.
- 7.12. The Committee considered that there was a variety of studies with varying patient population characteristics. The Committee noted that some studies excluded patients who had had a recent myocardial infarction, acute coronary syndrome, or similar cardiovascular conditions, while the EMPA-REG OUTCOME required established cardiovascular disease – the definition of which included a history of myocardial infarction or stroke, evidence of multi-vessel and single vessel coronary artery disease, unstable angina, and occlusive peripheral artery disease.
- 7.13. The Committee noted that the EMPA-REG OUTCOME was designed as a safety trial, not an efficacy trial. The Committee noted that it reported improvements over placebo in death from any cause, death from cardiovascular causes, hospitalisation for heart failure, and the study's composite endpoint. However, members considered it did not demonstrate improvements in all other measured outcomes, such as rates of myocardial infarction, cerebrovascular accident, transient ischaemic attacks, revascularisation, or admission for unstable angina.
- 7.14. The Committee noted that the EMPA-REG OUTCOME study (1245.26) reported an improvement over placebo in several renal outcome measures.
- 7.15. The Committee noted that all trials were industry sponsored and did not provide head to head comparisons with other antidiabetic agents. The Committee considered that, based on currently published evidence, empagliflozin provided greater improvement in baseline HbA1c when compared with placebo, and was non-inferior compared with other agents such as sitagliptin or glimepiride.

- 7.16. The Committee considered that empagliflozin led to improved weight reductions when compared with other agents, and lower blood pressure when compared with sulfonylureas, but that empagliflozin's adverse effects include urinary tract infection, genital infection, and in rare cases hypoglycaemia. The Committee considered the costs of managing these adverse events could be significant.
- 7.17. The Committee considered that there was moderate evidence for improved cardiovascular and renal outcomes for patients with type II diabetes and established cardiovascular disease. The Committee considered that it was uncertain whether patients obtained cardiovascular risk benefits from continued empagliflozin treatment in the absence of reduced HbA1c levels, and if patients remained on treatment without these benefits it would adversely affect the cost-effectiveness.
- 7.18. The Committee considered that it is likely that empagliflozin, or any antidiabetic agent funded, would be taken as an additional treatment in combination with metformin but as a substituting replacement treatment for those on sulphonylureas.
- 7.19. The Committee considered that were empagliflozin, or any other antidiabetic agent, funded in New Zealand there would be a very high level of uptake in all eligible type 2 diabetic patients.
- 7.20. The Committee considered that the definition of established cardiovascular disease proposed by the supplier differed to the generally used definition in New Zealand clinical practice. Members considered it was important to refer to the trial evidence base and population definition to guide appropriate access criteria for a high cardiovascular risk population, but that this needed to be balanced with practicalities for its implementation in New Zealand and the potential to increase inequity of access.
- 7.21. The Committee considered it was currently uncertain whether there was a SGLT-2 inhibitor class effect with empagliflozin, as the evidence for cardiovascular outcomes for other SGLT-2 inhibitor agents had not yet been reviewed by PTAC. The Committee considered it would be appropriate to consider each agent individually with respect to its benefits in addition to improving glycaemic control. Members considered that there are likely few clinically meaningful differences between different SGLT-2 inhibitor agents.
- 7.22. The Committee considered that given a higher prevalence, and earlier age of onset, of cardiovascular disease and diabetes in both the Māori and Pacific populations, there would be potential for a greater absolute benefit in these patients from treatment with empagliflozin. However, the Committee acknowledged that as it would be difficult to provide access to ethnic groups specifically (apart from their higher preponderance in risk-based approaches), it would be important to consider these disparities when determining appropriate access criteria.

8. Rituximab for the treatment of neuromyelitis optica spectrum disorder (NMOSD)

Application

- 8.1. The Committee considered a clinician application for widening access to rituximab for the treatment of neuromyelitis optica spectrum disorder, in patients who do not respond to treatment with azathioprine or mycophenolate.

Recommendation

- 8.2. The Committee **recommended** that access to rituximab be widened to include treatment of patients with neuromyelitis optica spectrum disorder not responsive to oral agents, with a high priority.
- 8.3. The Committee **recommended** the following restrictions for rituximab when used for the treatment of neuromyelitis optica spectrum disorder, in patients who do not respond to treatment with mycophenolate:

Initial – (Neuromyelitis Optica Spectrum Disorder) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

1. The patient has experienced a breakthrough attack of NMOSD; and
2. Both:
 - 2.1 The patient is receiving treatment with mycophenolate; and
 - 2.2 The patient is receiving treatment with corticosteroids.

Note: Initial approval is for either 2 doses of 1,000 mg rituximab to be administered fortnightly, or for 4 doses of 375 mg/m² rituximab to be administered weekly for 4 weeks.

Renewal – (Neuromyelitis Optica Spectrum Disorder) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:

All of the following:

1. The patient has responded to the initial course of rituximab; and
 2. The patient has not received rituximab in the previous 6 months; and
 3. The patient's CD19 or CD27 levels have risen significantly.
- 8.4. The Committee **recommended** that rituximab for the first line treatment of patients with neuromyelitis optica spectrum disorder who present with an initial severe episode or relapse, be referred to the Neurological Subcommittee for review.
- 8.5. The Committee **recommended** that the Neurological Subcommittee review the evidence for use of first line tacrolimus for neuromyelitis optica spectrum disorder.
- 8.6. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 8.7. The Committee noted that neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorder (NMOSD) are inflammatory disorders of the central nervous system, characterised by severe, immune-mediated demyelination and axonal damage that predominantly target the optic nerves and spinal cord. The Committee noted that disease severity for NMOSD can be measured using the Expanded Disability Status Scale (EDSS) score, and that despite some similarities with multiple sclerosis (MS), people with NMOSD have a comparably worse quality of life than people with MS. The Committee noted that NMOSD was previously viewed as a variant of MS, however it is now considered a distinct disease on its own.
- 8.8. The Committee noted the paper by Bukhari et al. 2017 (J Neurol Neurosurg Psych;88:632-38) which reported an incidence rate of 0.37 per million per year and a prevalence of 0.70 per 100,000 for NMOSD in Australia and New Zealand. The Committee noted that NMOSD affects mostly young patients, with average age of onset of NMOSD being approximately 40 years, and that the disease disproportionately affects women (5:1 ratio). The Committee noted that NMOSD is associated with a high mortality rate, most frequently secondary to neurogenic respiratory failure. The

- Committee noted that NMOSD disproportionately affects people of African and Asian descent.
- 8.9. The Committee noted that people with NMO and NMOSD experience acute attacks of bilateral or rapidly sequential optic neuritis (leading to severe visual loss) or transverse myelitis (often causing limb weakness, sensory loss, and bladder dysfunction) with a typically relapsing course. The Committee noted that these attacks most often occur over days, with variable degrees of recovery over weeks to months. The Committee noted that relapses of disease are treated with high dose corticosteroids, intravenous immunoglobulins, and/or plasma exchange, over a period of several weeks, and that each relapse incurs significant expenditure for the health service. The Committee also noted that any relapse is potentially severe or fatal, and may leave the patient with high residual disability post-relapse.
- 8.10. The Committee noted that there would likely be significant burden on the family, whānau, and informal caregivers of people with NMOSD. The Committee noted the relatively worse quality of life of people with NMOSD than MS, and considered that it would be likely that the burden on family, whānau, and caregivers would also be worse for NMOSD than MS. The Committee noted that both blindness and neuromuscular symptoms and the subsequent disability caused by NMOSD would cause caregivers to experience higher levels of distress and a reduced quality of life.
- 8.11. The Committee noted that earlier, and more severe relapses or episodes of the disease, are associated with worse outcomes in patients with NMOSD. The Committee noted that the prevention of relapse is an important goal of treatment, and considered that the prevention of relapse and breakthrough attacks could lead to reduced patient morbidity and mortality.
- 8.12. The Committee noted that currently funded pharmacological treatments for the prevention of NMOSD relapses include the use of oral immunosuppressants such as corticosteroids, azathioprine, and mycophenolate, and that these medicines would usually be used indefinitely.
- 8.13. The Committee considered the following papers as evidence supporting the use of rituximab in this indication:
- Nikoo et al. *J Neurol*. 2017;264:2003-9
 - Damato et al. *JAMA Neurol*. 2016;73:1342-8
 - Jeong et al. *Mult Scler*. 2016;22:329-39
 - Kim et al. *JAMA Neurol*. 2013;70:1110-7
 - Zephir et al. *J Neurol* 2015;262:2329-35
 - Zhang et al. *Acta Neurol Belg* 2017;117:695-702
 - Torres et al, *J Neurol Sci*, 2015;351:31-5
 - Kim et al. *Mul Scler* 2017;1-7, DOI:10.1177/1352458516687403
 - Mealy et al. *JAMA Neurology* 2014;71:324-30
 - Annovazzi et al. *J Neurol* 2016;263:1727-35
 - Collins et al. *Mult Scler*. 2016;22:1349
- 8.14. The Committee noted the systematic review and meta-analysis by Damato et al. 2016 which reviewed 25 papers (from 1 January 2000 to 31 July 2015) that studied the effects of rituximab on changes to the EDSS score in NMOSD. The Committee noted a reported mean change in EDSS of 0.64 with rituximab treatment. The Committee considered that this value may be conservative, as more recent trials reported an average change in EDSS score of approximately 2.0 after treatment with rituximab. The

- Committee noted Collins et al. 2016, reported a change in EDSS of > 1.0 can be considered as clinically meaningful. The Committee considered that the evidence for the use of rituximab in this indication was of moderate quality, and was of high strength.
- 8.15. The Committee considered the paper by Annovazzi et al. 2016, which reviewed the different dosing regimens for rituximab. The Committee considered that there was no significant difference in terms of outcome when patients were initiated on treatment with either 2 x fortnightly doses of rituximab 1000mg, or 4 x weekly doses of rituximab 375mg/m².
 - 8.16. The Committee noted the restrictions proposed by the applicant for rituximab for the treatment of NMOSD. The Committee noted that the proposed restrictions would require patients to have tried oral treatments with either mycophenolate or azathioprine prior to becoming eligible for treatment with rituximab. The Committee considered that current evidence indicated that mycophenolate was probably superior to azathioprine for treating NMOSD, and therefore considered that the restriction should be amended to require patients to have tried mycophenolate, rather than either mycophenolate or azathioprine. The Committee considered that the change in wording would guide clinicians to use mycophenolate rather than azathioprine for the treatment of this disease.
 - 8.17. The Committee noted that there are studies reporting the effectiveness of tacrolimus when used in the prevention of NMOSD relapses, however noted the lack of head to head comparison trials against mycophenolate. The Committee **recommended** that the Neurological Subcommittee review the evidence for use of tacrolimus as first line treatment for neuromyelitis optica spectrum disorder, with a view to potentially widen access to tacrolimus for this indication.
 - 8.18. The Committee considered that further advice should be sought from the Neurological Subcommittee to quantify appropriate increases for the proposed renewal criteria which require a significant rise in either CD19 or CD27 levels.
 - 8.19. The Committee noted that relapses of disease often required acute intervention with high dose corticosteroids with or without the need for plasma exchange therapy depending on whether the patient has refractory disease. The Committee considered that each relapse/ episode of NMOSD is associated with high treatment costs, which could be offset by rituximab.
 - 8.20. The Committee noted that patients who present with an initial severe attack or relapse of NMOSD may have residual disability, and considered these patients to be of high risk. The Committee noted that severe relapse was defined as an EDSS score of ≥ 6 (requiring a walking aid to walk 100 m with or without resting), or an increase of ≥ 0.5 points if the patient had a baseline EDSS score of ≥ 6 , or in the case of optic neuritis a new worsening of visual acuity (VA) of ≤ 0.1 in patients with a baseline VA of > 0.1 . The Committee considered that due to the severity of the initial attack and the high morbidity and subsequent risks of relapse, that these patients may benefit from rituximab first line without the need to first trial oral agents. The Committee **recommended** that rituximab for the first line treatment of patients with neuromyelitis optica spectrum disorder who present with an initial severe episode or relapse, be referred to the Neurological Subcommittee.
 - 8.21. The Committee considered that there would likely be around 75 patients in New Zealand who might meet the eligibility criteria of being treated with rituximab for NMOSD not controlled by mycophenolate.

- 8.22. The Committee **recommended** that access to rituximab should be widened to the treatment of NMOSD with a high priority, on the basis of a high unmet health need associated with the disease, the evidence that rituximab has a high treatment effect in the prevention of NMOSD relapses, and the high healthcare costs that treating with rituximab is likely to offset to the health system.

9. Multiple Sclerosis Treatments Widening Access

Application

- 9.1. The Committee considered an application from Multiple Sclerosis New Zealand for widening access to multiple sclerosis treatments in four settings: including Clinically Isolated Syndrome (CIS), amending stopping criteria to EDSS 6.5, amending the definition for 'significant relapse' and using an alternative measurement scale to better assess fatigue and cognition.

Recommendation

- 9.2. The Committee **recommended** that widening access by including patients with Clinically Isolated Syndrome who fulfil the McDonald 2010 diagnostic criteria for MS (but without the additional requirement to experience significant relapse in the last 12 months) be declined.
- 9.3. The Committee **deferred** making a recommendation about amending the definition of 'significant relapse' in the Special Authority criteria to shorten the duration from at least one week to 24 hours, and requested the Multiple Sclerosis Treatments Advisory Committee (MSTAC) provide its view for PTAC to consider.
- 9.4. The Committee **deferred** making a recommendation about widening access by amending the stopping criteria to EDSS 6.5 for all patients, irrespective of EDSS score at entry. The Committee requested MSTAC be asked to provide its view on this issue.
- 9.5. The Committee **recommended** that widening access by including the use of an additional measurement scale be declined. The Committee however requested that MSTAC provide its view on whether cognitive assessment should be included in the Special Authority criteria.

Discussion

- 9.6. The Committee noted that PHARMAC currently funds a number of multiple sclerosis (MS) disease modifying treatments (DMTs). These comprise 'newer' treatments: natalizumab (Tysabri), fingolimod (Gilenya), dimethyl fumarate (Tecfidera) and teriflunomide (Aubagio); and 'older' treatments: interferon beta-1a (Avonex), interferon beta-1b (Betaferon) and glatiramer acetate (Copaxone).
- 9.7. The Committee noted that MS treatments have undergone extensive review by both PTAC and the Neurological Subcommittee. Most recently, in November 2014, the access criteria were substantially changed and two newer treatments (natalizumab and fingolimod) were funded. The funding changes were in line with PTAC's advice. In February 2016 two other treatments were also funded (dimethyl fumarate and teriflunomide).

Widening access to include Clinically Isolated Syndrome

- 9.8. The Committee noted that in February 2014 PTAC had reviewed its earlier recommendation to decline funding for CIS fulfilling the McDonald 2010 diagnostic criteria, and that PTAC had agreed with the Neurological Subcommittee that there was

no robust evidence from randomised controlled trials to support the use of fingolimod or natalizumab in patients with clinically isolated syndrome but that evidence may emerge in the future. The Committee noted its comments that treating patients after a single demyelination episode (in a clinically isolated syndrome), but before a diagnosis of definitive MS had been made, would risk unnecessarily treating some patients who do not progress to/go on to develop definite MS. (PTAC minutes February 2014 paragraphs 5.8, 5.23, web version <https://www.pharmac.govt.nz/assets/ptac-minutes-2014-02.pdf> 2.8, 2.23).

- 9.9. Members considered that the new evidence provided in support of the current application consisted of low quality evidence such as selected expert consensus statements and non-systematic evidence reviews that recommend early initiation, rather than high quality evidence such as randomised controlled trials (RCTs).
- The Committee considered the Association of British Neurologists (ABN) revised (2015) guidelines for prescribing DMT in MS (Scolding et al. *Pract Neurol*. 2015;15:273-9) had couched its recommendations for CIS in ways that were not definitive, where the ABN had stated “Neurologists may consider advising treatment [after individual risk/benefit discussion] or individuals within 12 months of a significant CIS, if MRI evidence established a diagnosis of MS” and “Various disease-modifying treatments can delay the diagnosis of MS in patients with CIS, though there is less secure evidence for their evidence of long-term benefit”. The Committee also noted the ABN’s use of the primary outcome of time to develop CDMS (Clinically Definite Multiple Sclerosis). The Committee considered five randomised controlled trials published between 2000 – 2014:
 - PreCISe study: Comi G et al. *Lancet* 2009;374:1503-11. Effect of glatiramer acetate on conversion to clinically definite MS in patients with clinically isolated syndrome;
 - ETOMS study: Comi G et al. *Lancet* 2001;357:1576-82 Effect of interferon beta-1a treatment on conversion to definite MS;
 - CHAMPS study: Jacobs et al, *N Eng J Med* 2000;343:898-904. IM interferon beta-1a therapy initiated during a first demyelinating event in MS;
 - BENEFIT study: Kappos et al. *Neurology* 2006;67:1242-9. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with CIS;
 - TOPIC study: Miller et al. *Lancet Neurol*. 2014;13:977-86. Oral teriflunomide for patients with a first clinical episode suggestive of MS.
- 9.10. The Committee noted that four of these trials predated the most recent revision in 2010 to the McDonald diagnostic criteria for MS.
- 9.11. The Committee considered a Cochrane Review relevant to CIS (Filippini et al. Treatment with disease-modifying drugs for people with a first clinical attack suggestive of multiple sclerosis. *Cochrane Database of Systematic Reviews* 2017: CD012200). Members noted that the systematic review reported 7 RCTs with the outcome of time to conversion to CDMS, which included the 5 RCTs listed above. The Committee noted that overall there was a significant advantage of early treatment of MS with DMTs, compared to control, in reducing the risk of developing CDMS during the first 24 months of treatment.
- 9.12. The Committee however considered that time to conversion to CDMS is not an appropriate primary outcome measure. Members noted that it is an intermediate outcome whereby it is hypothesised that increasing time to conversion to CDMS results

in less pathological damage and better long term functional status, but considered that the evidence does not indicate that preventing recurrent attacks delays the progression of disability. Members noted that the large epidemiological prognostic registry studies report wide variability in long-term disability worsening, even in those patients with frequent relapses. The Committee also reiterated that treating patients after a single demyelination episode (in CIS), but before a diagnosis of definitive MS had been made, risked unnecessarily treating some patients who do not progress to/go on to develop definite MS.

- 9.13. The Committee considered the quality of evidence to be low to very low, with a high risk of bias, and that reporting of adverse events was rare.
- 9.14. The Committee considered that there was considerable uncertainty around benefits and harms with treating CIS, with probably no additional health benefit with regard to the primary outcome of disability worsening, although there was probably a small health benefit in terms of relapse reduction acutely (with short-term effects). The Committee considered that there may be an additional harm when compared with current access criteria, as 15% of patients do not go on to develop CDMS. The Committee noted that the evidence provided was largely for the older second line treatments.
- 9.15. The Committee considered again that overall there was currently insufficient evidence to support widening access to DMTs for CIS but that it would like to review this recommendation should new, good quality, evidence become available. The Committee noted that good quality evidence would include RCTs and meta-analyses, but not consensus statements.

Definition of Significant Relapse

- 9.16. The Committee noted that all MS Special Authorities include the starting requirement for patients to have experienced at least 1 significant relapse in the previous 12 months or 2 significant relapses in the past 24 months, as well as a requirement that a significant relapse must last at least one week.
- 9.17. The Committee considered the evidence provided by the applicant in support of the proposal to change the definition of a significant relapse:
 - Proceedings of a CMSC Consensus Conference. *Int J MS Care* 2014;16:1-36.
 - Polman et al. *Ann Neurol* 2011;69:292-302.
- 9.18. The Committee noted that the application did not provide any direct evidence to support a change in the definition of a significant relapse, but noted that the definition used in New Zealand differs from that used internationally.
- 9.19. The Committee noted that the original definitions of significant relapse in the 1983 Poser et al. (*Ann Neurol.* 1983;13:227-31), 2001 McDonald et al. (*Ann Neurol.* 2001;50:121-7), 2005 Polman et al. (*Ann Neurol.* 2005;58:840-6), and 2011 Poser et al. (*Ann Neurol.* 2011;69:292-302) criteria contained no epidemiologic or literature-based explanations behind the definition of 24 hours with a prior 30-day symptom free period.
- 9.20. The Committee considered three recent trials of MS treatments:
 - Kappos et al. *N Eng J Med* 2010;362:387-401. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. (Patient review by neurologist at 7 days)
 - Polman et al. *N Eng J Med* 2006;354:899-910. A randomised, placebo controlled trial of natalizumab for relapsing multiple sclerosis. (Patient review by neurologist at 5 days)

- O'Connor et al. N Eng J Med 2011;365:1293-1303. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. (Patient review by neurologist at 7 days)
- 9.21. The Committee considered that in recent literature, there has been no consistent period used to define a relapse. In these studies, the relapse period could be taken as the time for review of symptoms by a neurologist, which was either at 5 or 7 days.
- 9.22. The Committee noted concern that changing the definition of significant relapse would potentially affect the application of stopping criteria for MS treatments (where having lower thresholds to defining relapses would mean “relapse” rates would rise despite no change in true relapse burden experienced, thus increasing chances of needing to stop funded treatment because relapse reductions were now less likely).
- 9.23. The Committee requested that MSTAC be asked to provide its view on the effect of amending the definition of significant relapse would have on patients starting and also stopping MS treatments. Members requested that MSTAC also be asked to provide its view on what proportion of patients would present with a symptom duration of less than 7 days and what additional proportion of patients would be likely to reach the current stopping criteria if the definition of significant relapse was amended to at least 24 hours’ duration.

Amending the stopping criteria to EDSS 6.5 for all patients

- 9.24. The Committee noted that in February 2014 PTAC had reviewed the Neurological Subcommittee’s proposed treatment algorithm which included stopping of the EDSS score progressed by various steps or having reached a maximum of 4.5, and that the Committee had agreed with the Neurological Subcommittee’s recommendations. (PTAC minutes February 2014 paragraphs 5.9, 5.19, webversion <https://www.pharmac.govt.nz/assets/ptac-minutes-2014-02.pdf> paragraphs 2.9, 2.19). The Committee further considered a draft minute from the July 2017 MSTAC meeting regarding this request to amend the stopping criteria. The Committee noted MSTAC members had considered that, as treating clinicians, their preference would be to treat all eligible people until EDSS 4.5 rather than treating those with CIS as proposed in this application from the MS Society.
- 9.25. The Committee noted that PHARMAC staff developed a complex cost effectiveness model to assess the fiscal impact of changes in the treatment algorithm. The Committee noted that the current access criteria were developed taking the available evidence into account, but also managing the fiscal risk and cost.
- 9.26. The Committee considered three trials provided by the applicant in support of amending the stopping criteria to EDSS 6.5:
- Lizak et al. J Neurol Neurosurg Psychiatry 2017;88:196-203.
 - Hauser et al. N Eng J Med 2017;376:221-34.
 - Scolding et al. Pract Neurol 2015;15:273-9.
- 9.27. The Committee noted that in Lizak et al (2017), the patterns of disability progression over time, following treatment, were highly variable in all the EDSS state groups (3 - 6, 4 - 6 and 6 - 6.5), so there still appeared scope for improvement to occur at any time for any individual patient. The Committee noted the significant disability that occurs with MS and that there would be a number of patients with a high EDSS who are not currently on treatment.

- 9.28. The Committee noted that since the establishment of the new access criteria at the time of listing fingolimod and natalizumab, several new agents have been listed, and the Committee considered it desirable for PHARMAC to revisit the criteria.
- 9.29. The Committee requested a number of stopping-based scenarios be modelled for cost effectiveness, in particular:
- all patients with established MS receiving MS treatments to EDSS 4.5
 - MS treatments (in established MS) to EDSS 6; and
 - MS treatments (in established MS) to EDSS 6.5
- 9.30. The Committee also invited PHARMAC staff to analyse and present any other options considered feasible for consideration by PTAC and MSTAC.
- 9.31. The Committee noted that the Association of British Neurologists 2015 guidelines (Scolding et al. 2015) do not rely on the EDSS score for stopping criteria.
- 9.32. The Committee requested MSTAC be asked for its views on:
- How likely treating clinicians would be to continue treatment with currently funded agents up to EDSS 6.5;
 - Whether recent improvements in MRI technology could potentially alter practice in the diagnosis of conversion to secondary progressive MS (SPMS), rather than relying on EDSS scores.

Use of an additional scale to assess effectiveness of treatment

- 9.33. The Committee considered a number of trials referenced in the application:
- Fischer et al. *Mult Scler* 1999;5:244-50.
 - Cutter et al. *Brain J Neurol* 1999;122:871-82.
 - Bin Sawad et al. *Curr Med Res Opin* 2016;32:1969-74.
 - Wynia et al. *Disabil Rehabil* 2008;30:261-74.
 - Schwartz et al. *Neurology* 1999;52:63-70.
- 9.34. The Committee also considered the BENEFIT study (Kappos et al. *Neurology* 2006;67:1242-9). The Committee noted that this trial in patients treated with an older agent used PASAT (Paced Auditory Serial Addition Test) scores. The patients had normal baseline cognitive status.
- 9.35. The Committee considered that the majority of randomised controlled trials on newer DMTs have not been appropriate to validly detect, quantify and monitor cognitive changes. Members noted that cognition had not been the primary outcome, and considered that observational studies on DMTs have been limited by being non-randomised, have included numerically small samples of patients with different clinical characteristics, have used heterogeneous cognitive assessment tools and outcome measures, and have not considered the patients' cognitive status at baseline.
- 9.36. The Committee considered the TYNERGY study (Svenningsson et al. *Plos One* 2013;8:1-8). The Committee noted this was an open-label, uncontrolled observational study in patients with relapse remitting MS (RRMS) with a mean EDSS of 3.2. Patients were reported to have small improvements in fatigue after 12 months, on a self-report fatigue questionnaire.
- 9.37. The Committee considered that no controlled studies have been reported that have primarily addressed the impact of DMTs on fatigue, and currently there is no consensus

regarding how therapies directed against the neuro-inflammatory component affect MS-related fatigue.

- 9.38. The Committee considered a range of measurement scales, and that they all have varying advantages and disadvantages:

Expanded Disability Status Scale (EDSS)

- 9.39. The Committee noted that confirmed change in EDSS has been, and remains, the primary clinically meaningful outcome for almost all MS trials of treatments' effectiveness in relapsing remitting MS. EDSS is used in RCTs for newer DMTs to measure the severity of the temporary (remitting) disability from relapses (where relapse frequency and severity is often the primary outcome measured in trials in relapsing remitting MS), as well as permanent (progressed) disability. Thus EDSS can be used to indirectly compare evidence for different and new treatments. Members noted NZ neurologists who treat MS are experienced in using the EDSS. The EDSS is based on a standard neurological examination that however is time consuming and subjective, with poor inter- and intra-rater reliability. Scores 4.0 – 7.5 are based primarily on the distance a patient can walk and the need for an assistance device. The Committee noted that EDSS does not capture cognitive performance, is a non-linear scale, and is difficult to use with visually impaired patients.

Multiple Sclerosis Functional Composite (MSFC)

- 9.40. The Committee noted that the MSFC appears to correlate with EDSS. A 20% change in the T25W (timed 25-foot walk) or the 9HPT (9 hole peg test) is thought to be clinically meaningful and 0.5SD for PASAT. MSFC has better inter- and intra-rater reliability than the EDSS. However, it is rarely used in clinical practice and to date has not been used to measure primary endpoints in RRMS RCTs of newer DMTs.

Multiple Sclerosis Impact Profile (MSIP)

- 9.41. The Committee noted that MSIP is a self-report scale assessing physical and psychological symptoms and covers a broad range of clinically relevant aspects of MS in 11 domains. It is based on the ICF (International Classification of Functioning, Disability and Health). MSIP appears to be both reliable and valid. It is a holistic and descriptive assessment of MS-related disability. However, there is no clinical trial evidence presented that newer DMTs improve MSIP.

Performance Scales (PS)

- 9.42. The Committee noted that PS is a self-report measure for MS-associated disability. It included the following eight domains: Mobility, Hand Function, Vision, Fatigue, Cognitive, Bladder/Bowel, Sensory and Spasticity Symptoms. The Committee considered it a valid, reliable, holistic and descriptive assessment of MS-related disability. However, the Committee noted that it is not used in clinical trials for DMTs.
- 9.43. The Committee considered Schwartz et al. (Health Qual Life Outcomes 2017;15:47), and noted that although the application had stated that "a recent review showed that 82 studies have used the tool in empirical research so far", only 5 of the studies reviewed by Schwartz et al involved an intervention and only 2 were RCTs. The Committee considered the risks with using self-reports to determine EDSS- or relapse-based stopping criteria leading to patients under-reporting symptoms in order to remain on treatment.
- 9.44. The Committee noted that EDSS-defined relapse is used to define end points in most DMT RCTs. The Committee considered that while self-report questionnaires might be

reliable and valid in observational studies, there is no evidence that validity of self-reporting is maintained when the scores determine treatment continuation (or discontinuation). The Committee considered that fatigue and cognition changes might appear earlier in MS than physical disability, however patients can currently start DMT treatments at EDSS 0 so therefore the lack of fatigue- or cognition-informed entry criteria would be unlikely to delay access to treatment. The Committee requested MSTAC be asked for its view on the need to consider adding cognitive function to the access criteria for DMT treatments.

- 9.45. The Committee also noted the emerging approach of using MRI scans to determine no evidence of disease activity (NEDA) as a diagnostic and monitoring tool for MS, and requested MSTAC be asked to advise on its relevance and applicability.

General discussion

- 9.46. The Committee noted that it was generally sympathetic towards the application for widening access to MS treatments, but considered that there was currently a lack of good quality evidence to support changes in access to MS treatments. However, the Committee considered that it would be appropriate to revisit the question of access to MS treatments if further good quality evidence became available. The Committee also considered it would revisit widened access to MS treatments following further cost-analysis by PHARMAC staff and advice from MSTAC.

10. Gaucher Disease Request for Funding Proposal

Conflicts of Interest

- 10.1. No additional interests were reported by Committee Members for the agenda item.

Application

- 10.2. The Committee reviewed a paper from PHARMAC staff regarding the Request for Proposals (RFP) for first line enzyme replacement therapy for Gaucher disease.

Recommendation

- 10.3. The Committee **recommended** that taliglucerase alfa be listed as the sole supply first-line enzyme replacement therapy for Gaucher disease for all patients (type 1 and type 3 Gaucher disease), noting it had considered a separate funding application for taliglucerase alfa.
- 10.4. The Committee **recommended** that if necessary it should be possible for a patient to switch back to imiglucerase for a clinical reason (i.e. no response or unable to tolerate taliglucerase alfa) approved by the Gaucher Panel as proposed in the RFP.
- 10.5. The Committee **recommended** that if taliglucerase alfa was awarded sole supply from the RFP, based on the commercial arrangements available, the Gaucher Panel should be able to determine the dosing of all Gaucher patients up to a maximum of 30 U/kg/every other week (or 60 U/kg/month) of taliglucerase alfa (or an alternative ERT if required).
- 10.6. The Committee **recommended** the Gaucher Panel be retained at this time, noting the Panel would have an important role in any transition if a change in first-line ERT was to occur.
- 10.7. The Committee **recommended** that any product change be supported by the transition plan proposed by PHARMAC staff.

Discussion

- 10.8. The Committee received the following information for review:
- PHARMAC discussion paper summary document regarding the RFP and preferred proposals
 - [RFP document](#) for first line enzyme replacement therapies (ERT) for Gaucher disease (GD)
- 10.9. The Committee noted the briefing paper from PHARMAC staff regarding the RFP for first line ERT for GD. Members noted the funding history of imiglucerase in New Zealand and their 2016 recommendation and minutes regarding velaglucerase alfa. Members noted that following this recommendation, PHARMAC had considered if it would be possible to change existing patients to a different Gaucher ERT treatment, and in August 2017 had released a RFP.
- 10.10. The Committee noted the comparative analysis provided by PHARMAC staff of the bids received and the possible options being considered regarding widened access to increased dosing for the different ERTs. The Committee considered there were no clinical reasons not to award sole supply for first line ERT to taliglucerase alfa. The Committee considered that PHARMAC should ensure patients could switch back to imiglucerase for clinical reasons (no response or unable to tolerate taliglucerase alfa) if necessary, as proposed in the RFP, and this should be approved by the Gaucher Panel. [Withheld].
- 10.11. The Committee reiterated its previous view that there was uncertainty around dosing of ERTs in GD and that long-term data regarding low dose use of ERT in GD, particularly regarding bone health, is unknown. Members noted the low-dose regimen currently used in NZ has been due to fiscal constraints and the high cost of imiglucerase. Members noted that the majority of patients currently on imiglucerase appear stable on a low-dose regimen and there is little evidence to suggest that these patients would benefit appreciably from an increased dose of ERT.
- 10.12. The Committee noted the pragmatic approach taken by PHARMAC staff to ensure competition even in the small NZ market for GD therapy and considered the RFP has provided opportunity to consider widening access to ERT for GD without necessarily increasing current expenditure.
- 10.13. The Committee noted that the Gaucher Panel had reviewed funding applications for taliglucerase alfa (November 2017) and velaglucerase alfa (May 2016) and considered either agent would be a suitable alternative ERT for all Gaucher patients currently on treatment in New Zealand, noting the more limited evidence base for taliglucerase alfa. [Withheld].
- 10.14. Members noted the approximately half of the patients currently on imiglucerase were self-cannulating or receiving ERT infusions at home. Members noted the Gaucher Panel had considered these patients would need to receive initial infusions for any new ERT in a hospital outpatient setting with close monitoring.
- 10.15. The Committee considered the proposed transition plans to support any treatment change for patients with GD were appropriate and that the Gaucher Panel had provided input into these plans.
- 10.16. The Committee noted the Panel acted as an independent body to manage dosing and provide clinical oversight and consistency. Members considered that the Gaucher Panel performs this role very well. Members noted the Gaucher Panel had a unique position in managing the significant fiscal risk of ERT for GD. The Committee **recommended** the Gaucher Panel be retained at this time, noting the Panel would have an important

role in any transition. The Committee considered a shift to a standard Special Authority restriction could be possible in the future if there was less fiscal uncertainty for Gaucher treatments.

10.17 Members noted historically ERT dosing for GD in New Zealand had been expressed in U/kg monthly doses, however members considered it may be less confusing to express dosing as fortnightly or every other week as this would be consistent with terminology in clinical trials and international practice.

11 Taliglucerase alfa for the treatment of Type 1 Gaucher's disease

Conflicts of Interest

11.13 No additional interests were reported by Committee Members for the agenda item.

Application

11.14 The Committee reviewed a funding application from Pfizer for taliglucerase alfa for the treatment of Gaucher disease. The application from the supplier was provided in response to PHARMAC's Request for Proposals (RFP) for first line enzyme replacement therapy for Gaucher disease.

Recommendation

11.15 The Committee **recommended** that taliglucerase alfa be funded for ERT in Gaucher disease only if cost-neutral to imiglucerase.

Discussion

11.16 The Committee received the following information for review:

- The application with all documentation provided by the applicant; and
- PHARMAC discussion paper summary document
- Previous PTAC and Gaucher panel minutes regarding imiglucerase and velaglucerase alfa
- Current imiglucerase access criteria
- Clinical evidence for taliglucerase alfa in Gaucher disease
- Cravo et al. Blood Cells Mol Dis 2017. pii:S1079-9796(16)30260-1
- Zimran et al. Blood Cells Mol Dis 2016. pii: S1079-9796(16)30087-0
- Zimran et al. Blood Cells Mol Dis 2016. pii: S1079-9796(16)30221-2

11.17 The Committee also reviewed the following material:

- Cochrane Database Syst Rev. 2015;(3):CD010324
- Viaro et al; Molecular Genetics and Metabolism 2015;114:S11-S130 (abstract only)

11.18 The Committee noted that Gaucher disease (GD), a lipid storage disease is a rare disorder that presents in patients in a range of phenotypes, and the clinical course and severity varies widely. Members noted that there are currently 20 patients receiving funded enzyme replacement therapy (ERT) with imiglucerase for GD in New Zealand, 18 patients with type 1 (GD1) and two patients with type 3 (GD3).

11.19 The Committee noted its 2016 recommendation and minutes regarding another ERT for GD, velaglucerase alfa.

11.20 The Committee noted that taliglucerase alfa was recently approved by Medsafe and the supplier had submitted the funding application to PHARMAC in anticipation of the RFP for first-line ERT for GD. Members noted that the supplier of taliglucerase alfa was only

interested in supplying this product in New Zealand in the proposed sole supply setting of the RFP.

- 11.21 The Committee noted that taliglucerase alfa is indicated for long-term ERT for patients with GD1 and is a recombinant human enzyme, produced in carrot cells. Members noted the approved indication for taliglucerase alfa did not include GD3, however this is also the case for velaglucerase alfa and until recently imiglucerase. Imiglucerase is now indicated for GD3 in some countries (not New Zealand) following the availability of post-market data in this patient group.
- 11.22 The Committee noted the evidence base for taliglucerase alfa is limited to real-world data, two randomised controlled trials (RCTs) and five non-randomised trials, with a small total number of patients (78) included in the trials. Members acknowledged this is to be expected for a rare disorder, particularly where there is only a small pool of patients not established on ERT worldwide.
- 11.23 The Committee noted the key published evidence in ERT naïve GD1 patients has been based on a randomised dose comparison phase 3 study in 32 adult patients ([Zimran et al. Blood. 2011;118\(22\):5767-73](#)) with two follow-up studies of extended treatment to up to 60 months ([Zimran et al. Blood Cells Mol Dis. 2015;54:9-16](#); [Zimran et al. Am J Hematol. 2016;91:656-60](#)). Members noted there are no head-to-head trials comparing taliglucerase alfa and imiglucerase.
- 11.24 The Committee noted the key evidence considered in patients switching ERT from imiglucerase to taliglucerase alfa comprised:
- an open label switching trial in 26 adult and 5 paediatric patients with subsequent follow-up to 36 months in 19 adults ([Pastores et al. Blood Cells Mol Dis; 2014;53:253-60](#); [Pastores et al. Am J Hematol; 2016;91:661-5](#));
 - an unpublished open-label study in 58 patients who switched to taliglucerase during the imiglucerase shortage;
 - an unpublished open-label retrospective observational study in 11 Australian patients treated with taliglucerase alfa either as continuation of therapy commenced within a clinical trial or to deliver therapy, during the global shortage of imiglucerase;
 - a retrospective efficacy and safety study reporting outcomes in 13 Brazilian patients, 12 switching ERT to taliglucerase alfa as the same dose as previous imiglucerase treatment ([Cravo et al. 2017](#)); and
 - a small prospective observational study (Brazil, 6 patients) that included quality of life information ([Viaro et al 2015](#)).
- 11.25 The Committee noted paediatric data demonstrating safety and efficacy of taliglucerase alfa in treatment naïve and patients switching from imiglucerase ([Zimran et al. Blood Cells Mol Dis 2016;Oct 20](#)). Members noted the sample size of 11 patients; two patients had type 3 GD. Clinically significant improvements were observed in haemoglobin concentration, platelet counts, spleen volume, and liver volume, and biomarkers. Three patients developed non-neutralising antibodies, however no association between antibodies and safety or efficacy was apparent. In treatment naïve patients, increases in growth parameters (height, weight, bone age) were age appropriate. Extension trial data for this group indicated maintained improvements.
- 11.26 Members noted that in general, efficacy and safety studies of switching to taliglucerase alfa had assessed clinical stability based on spleen volume, anaemia, thrombocytopaenia, liver volume and biochemical markers. Clinical trials for ERT for

- GD did not often assess the impact of ERT on bone disease, a significant clinical consequence of the disease for some patients. The median dose of taliglucerase alfa used in many of the considered studies was approximately 30 U/kg every other week (~ 60 U/kg/month). Overall, taliglucerase was well-tolerated when switching from imiglucerase and resulted in stability in measured clinical and laboratory parameters.
- 11.27 The Committee noted the health need of patients with GD varies widely. Symptomatic patients may die prematurely from the consequences of splenectomy, severe bone disease, bleeding, infection, liver failure, or severe pulmonary disease. Patients also appear to be at increased risk of haematological malignancy, especially B-cell lymphomas and multiple myeloma. The Committee noted the quality of life data for patients receiving ERT for GD was limited and given that GD covers a wide constellation of symptoms, this information would be useful. A US health-related quality of life study in 212 patients with GD since starting ERT reported fewer limitations in physical activities (53%), better general health perceptions (77%) and less negative emotion (49%) ([Damiano AM et al. Qual Life Res. 1998;7:373-86](#)).
- 11.28 The Committee considered overall the evidence was of moderate quality to indicate that taliglucerase alfa has a same or similar therapeutic effect as imiglucerase at the doses reported in the trials. Members noted evidence was of low quality for doses less than 30 U/kg/every other week. The Committee considered that, based on the limited and relatively immature evidence available, if patients switched from imiglucerase to taliglucerase alfa then taliglucerase alfa would have a similar or same effect at the same dose. Members noted New Zealand uses lower dosing of imiglucerase compared to other countries, and considered equivalent dosing may be possible with taliglucerase alfa based on extrapolation of dosing data, but evidence is very limited regarding this. Members considered determining a maximum dose would be a fiscal decision, and if significant price reductions were achieved then it could allow for higher U/kg dosing of taliglucerase alfa, particularly in those that would benefit most, such as younger patients. Members noted that due to the limited evidence available, it would be preferable that taliglucerase alfa be funded up to the doses reported in the efficacy data.
- 11.29 The Committee considered overall there would be no additional clinical benefit from taliglucerase alfa compared to current treatment with imiglucerase at the same dose. Members noted some patients may develop antibodies, some with neutralising activity in vitro, or experience hypersensitivity infusion reactions with taliglucerase alfa, but that the relationship between hypersensitivity reactions and antibody status is unclear. The Committee noted the adverse reaction data for taliglucerase alfa and imiglucerase and considered there may be some indications that hypersensitivity reactions were more common with taliglucerase alfa. However, due the very small patient numbers this is difficult to determine from the evidence available. Members noted that close monitoring of patients receiving initial infusions with taliglucerase alfa would be appropriate.
- 11.30 Members noted the 200 unit vial size of taliglucerase alfa was acceptable, and although half the size of the other ERT products this would not necessarily affect wastage due to current dose rounding facilitated by the Gaucher Panel.
- 11.31 The Committee noted the that Gaucher Panel has also recently reviewed the funding application for taliglucerase alfa, and the Panel had considered that taliglucerase alfa would be a suitable alternative ERT for all Gaucher patients currently on treatment in New Zealand, the Panel noting the limited evidence base. Members noted the minutes from this meeting were not yet available, however noted the key points reported from this discussion.