PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 22 May 2020 via videoconference

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ATTENDANCE

PTAC members:

Present
Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Bruce King
Giles Newton Howes
Jane Thomas
Jennifer Martin
Matthew Strother
Rhiannon Braund
Sean Hanna
Stephen Munn
Tim Stokes

Apologies
Simon Wynn Thomas

1. The role of PTAC, PTAC Subcommittees and meeting records

1.1. This meeting record of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

1.2. The PTAC Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC and PTAC Subcommittees.

1.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

1.4. PTAC and PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. PTAC may therefore, at times, make recommendations that differ from PTAC Subcommittees', including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC Subcommittees may, at times, make recommendations that differ from PTAC's, or from other PTAC Subcommittees', when considering the same evidence.

PHARMAC considers the recommendations provided by both PTAC and PTAC Subcommittees when assessing applications.

2. Ustekinumab for moderately to severely active ulcerative colitis

Application

2.1. The Committee reviewed the application from Janssen for ustekinumab for the treatment of moderately to severely active ulcerative colitis (UC) in adult patients who have experienced either: inadequate response to, intolerable side effects from, contraindications to, or loss of response from, infliximab.

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

Recommendation

2.3. The Committee **recommended** that ustekinumab be funded for patients with moderately to severely active ulcerative colitis (UC) in adult patients who have experienced either: inadequate response to, intolerable side effects from, contraindications to, or loss of response from, infliximab with a medium priority subject to the following Special Authority criteria:

> **USTEKINUMAB**
> **Initiation – moderately to severely active ulcerative colitis**
> Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 4 months.
> All of the following:
> 1. Patient has histologically confirmed ulcerative colitis; and
> 2. Patients is 18 years or older with a total score of 6 to 12 on the Mayo scale and an endoscopic subscore of 2 or 3; and
> 3. Patient has tried infliximab at an appropriate dose but received an inadequate response to (including lack of initial response and/or loss of initial response) or experienced intolerable side effects from prior treatment with infliximab; and
> 4. Surgery (or further surgery) is considered clinically inappropriate; and
> 5. Ustekinumab will be used at a dose of 130 mg for induction and used at a dose no greater than 90 mg subcutaneously every 8 weeks for maintenance.
>
> **Renewal – moderately to severely active ulcerative colitis**
> Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 6 months.
> All of the following:
> 1. Patient is continuing to maintain a response (see Note) and the benefit of continuing treatment with ustekinumab outweighs the risks; and
> 2. Patients is 18 years or older; and
> 3. Ustekinumab will be used at a dose no greater than 90 mg subcutaneously every 8 weeks.
>
> Note: Response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding sub score of ≥1 or a rectal bleeding subscore of 0 or 1.

2.4. In making this recommendation, the Committee considered the high health need of this patient group, the suitability of ustekinumab, which for maintenance can be administered subcutaneously, and the evidence of particular efficacy in patients who have previously experienced biologic failure. However, the Committee noted that in the report of the UNIFI trial the estimates of the differences of quality of life may not have been clinically meaningful, and that there were limitations of the evidence comparing the benefits of different treatments for UC.

Discussion

2.5. The Committee noted that ulcerative colitis (UC) is a chronic inflammatory bowel disease affecting the large intestine that usually follows a remitting-relapsing course, has varying disease activity and severity, and has a tendency to become refractory to, or not respond to, treatment. The Committee noted that clinicians in New Zealand generally use the Simple Clinical Colitis Activity Index (SCCAI) to assess UC disease activity, while the Mayo index (which requires endoscopic examination) is often used to measure UC outcomes in clinical trials. Members considered that an SCCAI score of four or greater, or a Mayo score of six or higher, indicates moderate disease activity.

2.6. The Committee noted that the incidence and prevalence of UC in New Zealand has been estimated to be 7.5 and 145 cases per 100,000 population, respectively, which corresponds to up to 7,250 New Zealanders living with UC (Gearry et al. Inflamm bowel dis. 2006;12:936-43); members considered these rates could slowly be increasing and that more patients are living with chronic UC.

2.7. The Committee noted that current standard of care treatment for patients with UC follows a stepwise approach, initially using pharmaceutical treatments including aminosalicylates (mesalazine and sulphasalazine), corticosteroids (prednisone), and immunomodulators (azathioprine and mercaptopurine). Treatment is escalated to include anti-TNF therapies

e.g. infliximab, for moderately to severely active UC that has not responded to earlier treatments, and then surgical resection if these treatments provide insufficient disease control. The Committee noted that response to a biologic therapy may delay colectomy, noting that UC often has a severe phase for the initial few years post-diagnosis with potential to abate, allowing a step down from biologic therapy if the patient has been adequately managed on biologics during the severe phase. However, the Committee considered that not all patients would proceed through all lines of funded therapy, as some may opt out of medical management at each step and proceed directly to surgery.

2.8. The Committee noted that infliximab is funded for first-line treatment of UC and the current Special Authority criteria allows for higher dosing as rescue therapy (to control disease flares) after 16 weeks. The Committee noted that the supplier estimated 700 people per year receive infliximab for UC, and the last Gastrointestinal Subcommittee advice (from May 2014) was that about 500 patients have moderate or severe UC that would be intolerant or refractory to other treatments and could be eligible for a second line biologic, if funded. The Committee considered that few of these patients would not be receiving treatment i.e. patients would either continue on infliximab or would proceed to surgery. Members considered that many patients would be on long-term maintenance infliximab treatment e.g. out to 3 years.

2.9. The Committee considered that approximately 30% of New Zealand patients who receive infliximab for UC achieve and maintain a response. The Committee estimated that between 5 and 10% of patients who experience a suboptimal response to infliximab may continue to meet funding criteria for renewal, and choose to continue infliximab as they are receiving sufficient benefit to warrant ongoing treatment.

2.10. The Committee considered that patients with moderately to severely active UC who have experienced either: inadequate response to, intolerable side effects from, contraindications to, or loss of response from, infliximab would have a high health need. Members considered that at least 50%, and potentially up to 80%, of patients who do not receive a response from infliximab will subsequently require surgery if no other medical options are available.

2.11. The Committee noted that some patients who proceed to colectomy may require up to 3 operations to achieve the final result. The surgical option will usually provide health benefits, but also carries risks of short- and long-term complications. The Committee considered it had seen no evidence about the incidence of colectomy for UC in New Zealand, however, members considered that colectomy rates are decreasing in some countries, partly driven by optimal use of thiopurines and the use of anti-TNF agents.

2.12. The Committee noted that ustekinumab is a monoclonal antibody directed against interleukin 12 and interleukin 23, naturally occurring proteins that regulate the immune system and immune-mediated inflammatory disorders. The Committee noted that ustekinumab is Medsafe-approved for the treatment of adult patients with moderately to severely active UC and for the treatment of patients with severe plaque psoriasis, patients with active psoriatic arthritis, and patients with moderately to severely active Crohn's disease (CD).

2.13. The Committee noted that ustekinumab has previously been considered by PHARMAC for the treatment of CD and for psoriasis, and that these proposals have been ranked. The Committee noted the differences in disease course and response to treatment for UC and CD, and noted that evidence for the use of ustekinumab in CD (reviewed by PTAC in May 2018, the Gastrointestinal Subcommittee in Oct 2018 and PTAC in Feb 2019) was based on the UNITI-1, UNITI-2 and IM-UNITI clinical trials conducted in biologic-naïve and biologic-experienced patients with CD; these studies also provide data for ustekinumab maintenance in CD.

2.14. The Committee noted that in clinical trials in UC the group randomised to placebo sometimes have a substantial reported response rate. Members noted that, based on the previously reviewed reports of the use of ustekinumab in CD, there was a 36% response

rate in participants who received induction treatment with ustekinumab and then placebo maintenance, compared with 53% in participants who continued on ustekinumab 8-weekly after induction treatment. Members considered that the proportion of patients with CD in long-term follow-up who were in remission was consistent with ongoing reduction in disease activity after ustekinumab induction.

2.15. The Committee noted the evidence from the phase 3, randomised (1:1:1), double-blind, placebo-controlled UNIFI trial of ustekinumab induction (intravenous ustekinumab 130 mg or 6 mg per kg dosing, or placebo) followed by maintenance in patients whose disease responded to induction therapy (subcutaneous ustekinumab 90 mg 8-weekly [q8w] or 90 mg 12-weekly [q12w], or placebo) in 961 patients with moderate to severe UC for whom other biologic or non-biologic therapies have failed (Sands et al. N Engl J Med. 2019;381:1201-14; also Supplementary Appendix).

2.16. The Committee noted that the UNIFI trial criteria required patients to have a baseline total score of six to 12 on the Mayo scale and subscore of two or three for the endoscopic component, with endoscopy required to confirm suspected loss of response to treatment. The Committee noted that more than half of patients (N = 491) with moderate to severe UC had experienced failure of at least one biologic treatment, and many patients received ustekinumab third-line (N = 160) due to previous use of vedolizumab as well as infliximab or other anti-TNF agent. The Committee noted that delayed response to induction was common and patients who experienced this had the option to enter maintenance at 16 weeks.

2.17. The Committee noted that the primary endpoint of the UNIFI trial was clinical remission after induction at week 8 (defined as a total Mayo score of two or less, and no subscore greater than one) which was reported to have been achieved in 15.6% (50/320) of patients who received ustekinumab 130 mg compared with 15.5% (50/322) who received ustekinumab 6 mg per kg compared with 5.3% (17/319) who received placebo (P<0.001 for each compared with placebo). The Committee considered that clinical remission was a challenging endpoint to achieve.

2.18. The Committee noted that clinical response at 8 weeks (defined in the UNIFI trial as a decrease from baseline in the Mayo score by 30% or greater and three or more points from baseline, with either a decrease from baseline in the rectal bleeding sub score of one or more, or a rectal bleeding subscore of zero or one) was 51.3% (130 mg), 61.8% (6 mg per kg) and 31.3% (placebo) for the three patient groups (P<0.001 for each compared with placebo).

2.19. The Committee noted that, in the UNIFI maintenance setting, clinical remission at week 44 (defined as Mayo stool frequency score of zero or one, with rectal bleeding subscore of zero) was 38.4% (66/172) for patients who received ustekinumab 90 mg q12w compared with 43.8% (77/176) in patients who received ustekinumab 90 mg q8w compared with 24.0% (42/175) who received placebo (P=0.002 and P<0.001, respectively, compared with placebo), and clinical response was maintained through week 44 in 68.0% (90 mg q12w) compared with 71.0% (90 mg q8w) and 44.6% of patients who received placebo (P<0.001 for each compared with placebo). The Committee considered that the response rate in the placebo group was very high and considered it was likely driven by a carryover effect of ustekinumab induction doses.

2.20. The Committee noted the outcomes of the UNIFI trial's secondary endpoints at 44 weeks of endoscopic remission (43.6% with 90 mg q12w compared with 51.1% 90 mg q8w compared with 28.6% for placebo; P=0.002 and P<0.001, respectively, compared with placebo) and steroid-free clinical remission 37.8% for 90 mg q12w compared with 42.0% for 90 mg q8w compared with 23.4% for placebo (P=0.002 and P<0.001, respectively, compared with placebo). The Committee considered that these were good results for endpoints that are challenging to achieve, and that steroid-free clinical remission is a highly relevant endpoint from a clinical perspective.

2.21. The Committee noted the UNIFI trial outcomes for clinical remission at 44 weeks in patients who experienced previous failure of biologics were 22.9% with 90 mg q12w compared with 39.6% 90 mg q8w compared with 15% for placebo *(P*<0.001 and *P*=0.044, respectively, compared with placebo); outcomes in patients who did not experience previous failure of biologics were 49% with 90 mg q12w compared with 48.2% 90 mg q8w and 31% for placebo *(P*=0.020 and *P*=0.024, respectively, compared with placebo) (Sands et al. J Crohn's Colitis. 2019;13(Suppl_1):S256-7). The Committee noted that clinical response at 44 weeks in patients who had experienced biologic failure was 55.7% with 90 mg q12w compared with 64.8% 90 mg q8w compared with 38.6% for placebo *(P*=0.008 and *P*<0.001, respectively, compared with placebo), and in patients who had not experienced biologic failure was 76.5% with 90 mg q12w compared with 77.6% 90 mg q8w compared with 50.6% for placebo *(P*<0.001 for each, respectively, compared with placebo).

2.22. The Committee noted that Inflammatory Bowel Disease Questionnaire (IBDQ) scores in UNIFI were low at baseline (126 for ustekinumab and 127 placebo; and 174 in both groups at maintenance baseline) and noted that a 20-point improvement was achieved in 61% of ustekinumab 6 mg per kg patients compared with 37% of placebo patients at 8 weeks; and 20-point improvements in scores were achieved and maintained at 44 weeks in 70% and 71% of ustekinumab q8w patients, respectively, compared with 43% and 50% of placebo (Sands et al. J Crohn's Colitis. 2019;13(Suppl_1):S460). The Committee considered that these results indicate some change in quality of life with ustekinumab treatment, however, noted that the estimates of differences in quality of life data did not reach clinical significance according to the established minimal clinically important difference (MCID) for quality of life in UC. However, Members considered that it was possible that ongoing treatment might be associated with further improvements in patient related outcomes.

2.23. The Committee noted that UC-related hospitalisations in the UNIFI trial at 8 and 44 weeks were reported in 0.6% (2) ustekinumab patients compared with 4.4% (14) placebo patients, respectively, and considered these results were encouraging although they were based on small patient numbers.

2.24. The Committee noted that there was evidence from the UNIFI trial suggesting that there is a relationship between serum ustekinumab concentration and clinical remission, however, there was no evidence for therapeutic benefits from monitoring target serum concentration levels of ustekinumab. The Committee noted that steady states were achieved after the first few doses of ustekinumab and that serum concentration was unaffected by prior or concomitant immunomodulator use (Adedokun et al. Clin Gastroenterol Hepatol. 2019;S1542-3565:31403-X [Epub ahead of print]). Members noted that the trough concentrations for 8-weekly to 12-weekly dosing demonstrated higher trough concentrations with 8-weekly dosing, although remission rates were generally similar (except for patients whose 12-weekly dosing trough levels were in the bottom quartile who had lower remission rates).

2.25. The Committee noted the results of the UNIFI long-term extension study, which provides long-term data for UNIFI patients who remained in the same randomised groups but were able to undergo dose adjustment from 12-weekly to 8-weekly dosing, and sham adjustment from 8-weekly to 8-weekly (Panaccione et al. J Crohn's Colitis. 2020;14(Suppl_1):S049; Sands et al. J Crohn's Colitis. 2020;14(Suppl_1):S476-7; Danese et al. J Crohn's Colitis. 2020;14(Suppl_1):S403). The Committee noted that the proportion of patients with symptomatic remission (assessed by an abbreviated Mayo) after two years indicated good maintenance of response even in patients who had experienced biologic failure.

2.26. The Committee noted that there was evidence of delayed response to ustekinumab 6 mg per kg induction in a proportion of patients in the UNIFI trial, with 209 of 322 patients responding at 8 weeks and 67 responding at 16 weeks (77.6% of patients responded to induction if delayed responders are included). Members considered that these patients had a genuine response at 16 weeks and that the data indicated their response would be maintained.

2.27. Members noted that the UNIFI long-term data could provide information as to whether there was greater benefit from 12-weekly or 8-weekly dosing on symptomatic remission rates, however, noted that about a quarter of patients in the long-term extension on q12w dosing had adjusted to q8w based on clinical criteria.

2.28. The Committee noted that, after 2 years further follow-up in the UNIFI trial, there were no concerning safety signals for serious infections or malignancy. Members noted that additional data regarding ustekinumab in pregnancy (indicated for treatment of CD, psoriatic arthritis and plaque psoriasis) indicates that it is safe and there were no indications of miscarriage or congenital abnormalities (Mahadevan et al. Gastroenterology. 2007;133:1106-12).

2.29. The Committee also noted the following conference abstracts (many from the ECCO Congress - European Crohn's and Colitis Organisation) regarding the UNIFI trial:

- Li et al. J Crohn's Colitis. 2019;13(Suppl_1):S008-9
- Van Assche et al. J Crohn's Colitis. 2019;13(Suppl_1):S054-5
- Sandborn et al. J Crohn's Colitis. 2019;(Suppl_1):S350-1
- Sands et al. United European Gastroenterol J. 2018;6:1586-97
- Li et al. J Crohn's Colitis. 2019;13(Suppl_1):S073
- Sandborn et al. J Crohn's Colitis. 2019;13(Suppl_1):S025-6
- Danese et al. J Crohn's Colitis. 2019;13(Suppl_1):S311-2
- Danese et al. J Crohn's Colitis. 2019;13(Suppl_1);S061-2
- Ochsenkuhn et al. J Crohn's Colitis. 2019;13(Suppl_1):S298-9

2.30. The Committee noted the results of a network meta-analysis that indirectly compared randomised controlled trials reporting induction and maintenance efficacy of anti-TNFs (infliximab, adalimumab and golimumab), vedolizumab, tofacitinib or ustekinumab, of which six trials included patients with failure of prior biologics and patients without biologic failure (Welty et al. Curr Med Res Opin. 2020;36:595-606). The Committee noted that analyses were conducted for clinical response, clinical remission and endoscopic-mucosal healing, and that the response-based trials were recalculated to correspond to a treat-through design for comparison. The Committee considered that the results were consistent with a greater response after 1 year (in patients who had experienced prior failure of biologics) with ustekinumab compared with vedolizumab, and also for ustekinumab compared with adalimumab. Members noted that indirect comparisons may be subject to biased estimates of effect sizes.

2.31. The Committee noted that another network meta-analysis indirect comparison was consistent with ustekinumab and tofacitinib having a better effect than vedolizumab or adalimumab for inducing remission in patients with moderate to severe UC who have had prior exposure to anti-TNFs (Singh et al. Clin Gastroenterol Hepatol. 2020;S1542-3565:30044-6). Members again noted the inherent limitations of such indirect comparisons, with bias that may affect reported estimates of effect sizes.

2.32. The Committee noted that the evidence for ustekinumab for UC was principally based on one commercially sponsored pivotal trial, which the Committee considered appropriately designed and well conducted; and therefore considered the evidence was of moderate strength and quality. However, the Committee noted that the quality of life changes did not reach clinical significance and considered that the network meta-analyses conducted to assess benefits of treatments for UC had important limitations.

2.33. The Committee considered that the evidence suggests ustekinumab is effective in patients who experienced previous failure of biologics i.e. second line use, with response rates close to that achieved in biologic-naïve patients.

2.34. The Committee considered that achievement and maintenance of response would correspond to treatment persistence and may reduce the risk of needing surgical treatment, or may delay time to surgical treatment. The Committee considered that reduction in risk of

surgery or delay in time to surgery is an important and relevant outcome for patients with UC. The Committee considered that remission may be used as a surrogate for avoidance of surgery and would be a desirable outcome, but noted that it is more challenging to see direct estimates of this outcome in relation to ustekinumab treatment.

2.35. The Committee considered that 8-weekly dosing of ustekinumab would be strongly preferred by patients and clinicians, and that dose escalation from 12 weekly to 8-weekly would be highly likely.

2.36. The Committee considered that the less frequent, 8 or 12 weekly self-administration of ustekinumab maintenance would be an advantage over fortnightly self-administered sub-cutaneous adalimumab, and over infliximab and vedolizumab which are both given intravenously and require treatment in a hospital setting.

2.37. The Committee considered that the target population and optimal place for ustekinumab in the UC treatment paradigm would be sequential to infliximab i.e. after infliximab, in patients for whom infliximab has provided an inadequate response, intolerable side effects, is contraindicated, or who have experienced a loss of response. The Committee considered that approximately 40% to 50% of patients who have received infliximab for two years would likely be eligible for ustekinumab, if funded, and therefore the number of patients who may be eligible for treatment would be lower than the supplier estimates, with uptake more likely to be approximately 150 to 200 patients per year.

2.38. The Committee considered that it would be appropriate for the Special Authority criteria for ustekinumab to use the Mayo score; the full Mayo score for initial approval and partial Mayo score for renewal. Members considered that colonoscopy would be commonly performed to confirm loss of response to infliximab and the need for an alternative agent and that the full Mayo score is considered to be a more accurate assessment of moderate to severe UC. Members considered that it would be appropriate for response to be assessed after 16 weeks, based on the evidence for delayed responders.

3. Modafinil for the treatment of excessive daytime sleepiness in obstructive sleep apnoea

Application

3.1. The Committee reviewed the application for Modafinil for the treatment of excessive daytime sleepiness in obstructive sleep apnoea.

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

Recommendation

3.3. The Committee recommended that modafinil for the treatment of excessive daytime sleepiness in obstructive sleep apnoea be declined due to:

3.3.1. Insufficient evidence regarding the long-term efficacy and safety of modafinil

3.3.2. A lack of meaningful clinical endpoints to measure efficacy benefit over time

3.3.3. The risk of diversion and off-label use

3.4. When making this recommendation, the committee noted the withdrawal of modafinil for excessive daytime sleepiness in obstructive sleep apnoea by the European Medicines Association (EMA) due to an unfavourable risk-benefit profile.

3.5. The Committee also considered that other potential treatments e.g. dietary modification, bariatric surgery, could be provided to patients for treatment of underlying obesity as the

leading driver of obstructive sleep apnoea, which may contribute to a reduction in the excessive daytime sleepiness experienced by this group of patients.

Discussion

3.6. The Committee considered a consumer application to fund modafinil for the treatment of obstructive sleep apnoea (OSA)-related excessive daytime sleepiness or OSA syndrome (OSAS). The Committee noted that the application was for patients who continue to experience excessive daytime sleepiness despite treatment with nasal continuous positive airway pressure (nCPAP).

3.7. The Committee noted that modafinil is Medsafe approved for this indication, and that there are currently no treatments for OSA-related excessive daytime sleepiness listed on the Pharmaceutical Schedule. The Committee noted that modafinil is currently funded in New Zealand for the treatment of narcolepsy. The Committee noted that modafinil is approved in several countries for narcolepsy and shift-work sleep disorder.

3.8. The Committee noted that OSA is caused by repetitive collapse or narrowing of the upper airways during sleep, resulting in repetitive breathing cessation (apnoea) or reduction (hypopnoea) typically paired with loud snoring.

3.9. The Committee noted that there are various risk factors for OSA, including obesity, narrowed airways, chronic nasal congestion, smoking, alcohol consumption, diabetes, being male, older age, high blood pressure, and a family history of OSA. The Committee noted that obesity is the most significant risk factor, and that the rates of obesity in New Zealand are increasing across all age groups, including children and adolescents. The Committee considered that this may lead to an increase in patients experiencing OSA and related daytime sleepiness in New Zealand in the future.

3.10. The Committee noted the various adverse effects of OSA, including excessive daytime sleepiness, impaired cognition, fatigue, anxiety, depression, and cardiovascular events. The Subcommittee noted a study by Gander et al. (N Z Med J. 2010;123:13-23) indicating that excessive daytime sleepiness resulting from OSA can lead to an increase in motor-vehicle and workplace accidents, and that patients with untreated, moderate to severe OSA are deemed unfit to drive by the European Union.

3.11. The Committee noted another study which indicated that partners of OSA sufferers also experience a reduced quality of life (QoL) due to sleep disruption and fatigue, impaired daytime functioning, and mood disorders such as depression (Luyster FS. J Clin Sleep Med. 2017;13:467-477).

3.12. The Committee considered that the health need of OSA-related excessive daytime sleepiness patients is high.

3.13. The Committee noted a study by Mihaere et al. (Sleep. 2009;32:949–956), which estimated the prevalence of OSA-related excessive daytime sleepiness in New Zealand to be 12.5% of males and 3.4% of females between the ages of 30 and 59. The Committee considered that the prevalence is probably higher than this estimate due to the increased prevalence of obesity in New Zealand since the study was published in 2009. The Committee also noted that this study reported that rates of OSAS were higher for Māori men and women than for non-Māori, but noted that in the Wellington Community Study by the same authors, which adjusted for neck size (as a measure of obesity) and BMI, there were no significant differences in OSAS prevalence between the Māori and non-Māori populations (Mihaere et al. Sleep. 2009;32:949–956). The Committee noted that there is currently no data available for prevalence of OSAS in the New Zealand Pacific population but considered that the prevalence of OSAS in this population would also be elevated due to high rates of obesity.

3.14. The Committee noted that there are various measures available to assess a patient's degree of OSAS:

3.14.1. The Epworth Sleepiness Scale (ESS), which is a short questionnaire that asks respondents about their perceived likelihood of falling asleep in 8 different scenarios, such as sitting or travelling. The Committee noted a study by Patel et al. (Am J Respir Crit Care Med. 2018;197:961-963) indicating that a change of -2 to -3 in the ESS is the minimal difference required for improvement in excessive somnolence to be considered clinically significant. The Committee noted that an ESS score greater than 10 is indicative of excessive daytime sleepiness. The Committee considered that ESS scores are subjective and subject to significant variability.

3.14.2. The Multiple Sleep Latency Test (MSLT), which measures a patient's tendency to fall asleep at different times during the day by recording sleep/wake states in a laboratory as well as five day-time nap attempts. The Committee noted that a sleep latency of less than 8 minutes is consistent with evidence of excessive daytime sleepiness. The Committee noted that the MSLT can only be assessed in sleep centres, which are available in major centres, but not country wide.

3.14.3. The Maintenance of Wakefulness Test (MWT), which is an objective measure of a patient's ability to stay awake and alert during the day and consists of four sleep trials with 2-hour breaks between them. The Committee noted that a time of less than 8 minutes to fall asleep is indicative of difficulty maintaining wakefulness.

3.15. The Committee considered that other causes of excessive daytime sleepiness such as insufficient sleep, medication, depression, anxiety, and neurologic disorders must be excluded prior to treatment.

3.16. The Committee noted that there are various lifestyle modifications that may benefit patients with for OSAS weight loss, smoking cessation, and not consuming alcohol before bed. The Committee also noted that patients with mild to moderate OSA can benefit from using mandibular advancement splints. The Committee noted that patients with moderate to severe OSA also have the option of uvulopalatopharyngoplasty surgery and adenotonsillectomy but acknowledged that these surgical procedures are associated with potential perioperative morbidity and mortality. The Committee also considered that patients for whom obesity is the cause of OSA, and for whom nCPAP has been ineffective, may also benefit from bariatric surgery

3.17. The Committee noted that the current mainstay of treatment for patients with more severe OSA is nCPAP but considered that adherence to treatment needs to be optimised and monitored as the machine can be cumbersome and uncomfortable for patients to use while sleeping. The Committee noted that international data indicates that the prevalence of OSAS with adequate nCPAP treatment is between 6 and 14% (Pepin et al. Eur Respir J. 2009 ;33(5):1062-7, Gasa et al. J Sleep Res. 2013;22:389-97). The Committee considered that patients with excessive daytime sleepiness after nCPAP may be significantly higher than this estimate, but it is unclear if this relates to low treatment adherence or failure of the treatment to resolve patients' excessive daytime sleepiness.

3.18. The Committee noted that amphetamines have been used to treat sleep disorders in the past, but that none are currently funded for this indication. The Committee considered use of amphetamines to treat sleep disorders to be inappropriate due to the risk of abuse, dependence and addiction, tolerance, sleep interference, and significant cardiovascular risks.

3.19. The Committee noted that modafinil has a wakefulness promoting effect on the central nervous system (CNS), but that the exact mechanism of action is unknown, though it is thought to enhance dopamine signalling. The Committee noted that modafinil is dissimilar to other CNS stimulants in that it has negligible sympathomimetic activity and does not appear to interfere with night-time sleep patterns.

3.20. The Committee considered that there are various risks associated with use of modafinil including abuse potential, skin and hypersensitivity reactions, and off-label use. The Committee also noted a recent study, which indicated that exposure during the first trimester of pregnancy has been linked to congenital malformations (Damiker P, Broe A. JAMA. 2020;323:374-376).

3.21. The Committee considered that there is little long-term safety data available for modafinil in the treatment of OSAS, and noted that it considered an application for the treatment of mood disorders, psychoses, ADHD, drug dependency, and shift work sleep disorder with modafinil in 2014, and had recommended then the application be declined due to a lack of evidence of effectiveness and safety data.

3.22. The Committee noted that in 2011 the European Medicines Agency withdrew modafinil for OSA related excessive daytime sleepiness due to an unfavourable risk-benefit profile in light of relevant post marketing surveillance data.

3.23. The Committee noted three clinical trials and systematic reviews supplied by the applicant relating to the effectiveness of modafinil in the treatment of excessive daytime sleepiness:

3.23.1. Pack et al. Am J Respir Crit Care Med. 2014;164:1675-81: a double-blind, placebo-controlled, randomised control trial of 157 patients with OSA and evidence of residual excessive daytime sleepiness while using nCPAP who received modafinil (n=77, 200 mg per day, week 1; 400 mg per day, weeks 2 to 4) or placebo (n=80) for 4 weeks. The Committee noted that mean ESS scores were reduced with both modafinil and placebo at week 4 ($p<0.001$), which was indicative of a placebo effect. The Committee noted that mean changes from baseline ESS scores between treatment groups were significantly different ($p<0.001$). The Committee also noted that there was a significantly greater percentage of modafinil patients with normalised ESS at week 4 compared with placebo (51% and 27% respectively, $p<0.01$). The Committee noted that post hoc analysis reported that ESS scores below ten were only achieved in patients with mild to moderate OSAS, and that patients with severe disease (ESS greater than 15) did not reach scores below ten.

3.23.1.1 The Committee noted that patients in the modafinil arm had an improvement in MSLT scores, but considered that this difference may not be clinically significant, as there was no between-group difference in the percentage of patients who had normalised MSLT at greater than 10 minutes ($p=0.613$). The Committee also noted that both treatment arms did not differ from baseline in their nCPAP use or nocturnal polysomnogram parameters measured.

3.23.1.2 The Committee noted that the most common treatment related adverse events were headache (23 patients with modafinil compared with 11 patients with placebo) and nervousness (12 patients with modafinil compared with 3 patients with placebo), and that the overall rate of discontinuation due to adverse events were 14% for modafinil compared with 4% for placebo.

3.23.2. Schwartz et al. Chest. 2003;124:2192-9: an open-label trial of 125 patients with moderate to severe OSAS who experience residual sleepiness despite nCPAP use who were given 200 or 400 mg per day of modafinil for 12 weeks. The Committee considered that although patients in the modafinil arm did appear to have improvements in EDS compared with placebo, confidence intervals were wide and overlapped. The Committee considered that the proportion of patients rated as having clinical improvement with modafinil (93%) may be due to the high risk of bias with ESS due to the subjectivity of scoring. The Committee noted that there were statistically significant improvements in QoL scores ($p<0.001$) but considered that these differences may not be clinically meaningful. The Committee

noted that 6% of patients were reported to have had cardiovascular adverse events, even though modafinil is regarded as having minimal sympathomimetic effects.

3.23.3. Chapman et al. Eur Respir J. 2016; 47:1420-28: a 2016 systematic review and meta-analysis of 10 studies (n=1466) in which OSA patients with excessive somnolence despite nCPAP treatment received modafinil for ≥2 weeks. The Committee noted that treatment with modafinil reportedly improved ESS scores by 2.2 points (95% CI, 1.5 to 2.9) with moderate effect size (0.55; 95% CI, 0.38 to 0.73), but considered that the lower bound of this confidence interval was lower than the defined minimally important clinical difference for ESS score. The Committee noted that treatment with modafinil improved the maintenance of wakefulness by 3 minutes (95% CI, 2.1 to 3.8 minutes) with small effect size (0.33; 95% CI, 0.08 to 0.58). The Committee also noted that FOSQ scores in three of the studies improved by 1 point (95% CI, 0.6 to 1.4). The Committee noted that the meta-analysis highlighted the lack of long-term safety data.

3.24. The Committee noted one additional systematic review of 8 studies of the effectiveness of pharmacotherapy (including modafinil) in the treatment of OSA-related excessive daytime sleepiness, all of which were included in the Chapman et al. systematic review and meta-analysis (Avellar et al. Sleep Med Rev. 2016;30:97-107). The Committee noted that the review considered that there was moderate quality of evidence to support the use of modafinil to reduce excessive daytime sleepiness, but that there was no evidence of HRQoL improvement and that there was a high level of potential bias across all 8 studies. The Committee also noted that there were higher discontinuation rates amongst patients taking psychostimulants to treat their sleepiness.

3.25. The Committee considered that the data available for the effectiveness of modafinil in treating patients with OSA-related excessive daytime sleepiness is of low to moderate quality and demonstrates short-term ESS score improvements of up to 12 weeks, however there is limited data on long-term efficacy, safety, or benefits for the New Zealand OSAS patient population. The Committee considered that there was limited data for beneficial effects of modafinil on OSA-related excessive daytime sleepiness, depression and anxiety, motor vehicle accidents, work-place accidents and work absenteeism.

3.26. The Committee considered that there is a significant risk of adverse side-effects and off-label use of modafinil, as well as potential for abuse and diversion.

3.27. The Committee considered that there is a high health and equity need for Māori and Pacific populations in New Zealand in the context of OSA and excessive daytime sleepiness, especially due to high rates of obesity in these populations. The Committee considered that patients experiencing socioeconomic deprivation are less likely to seek secondary or tertiary care for their OSA and are therefore less likely to undergo the sleep studies needed to obtain treatment such as nCPAP. Additionally, the Committee considered that the inequity is heightened due to the variability in DHB funding criteria and the availability of sleep centres for sleep studies, which are a requirement prior to receipt of funded nCPAP machines. Thus, patients may need to visit private sleep clinics if services are not offered by their DHB. Furthermore, the committee considered that while the nCPAP machine may be funded for some patients, these patients are required to replace broken nCPAP machine parts at their own expense.

3.28. The Committee considered that despite the high health need for an appropriate treatment in this clinical setting, there is a significant lack of long-term data regarding the efficacy and safety of modafinil, as well as the risk of off-label use, abuse and diversion. In addition, the Committee considered the post marketing action by the EMA to remove the residual daytime sleepiness in OSA indication, due to the unfavourable risk-benefit profile, to be relevant and indicative of a lack of evidence that its use would be appropriate for this indication.