PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

Level 9, 40 Mercer Street, PO Box 10-254, Wellington 6143, New Zealand

Phone 64-4-460-4990 - Fax 64-4-460-4995 - www.pharmac.govt.nz

Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 18 September 2020

The records of PTAC and Subcommittees of PTAC are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016. Note that this document is not necessarily a complete record of the meeting; only the relevant portions of the record relating to discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

PTAC and Subcommittees of PTAC may:

a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule

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

Present:

PTAC members:
Mark Weatherall (Chair)
Alan Fraser
Brian Anderson
Bruce King
Elizabeth Dennett
Giles Newton Howes
Jane Thomas
Lisa Stamp
Matthew Strother
Rhiannon Braund
Sean Hanna
Simon Wynn Thomas
Stephen Munn
Tim Stokes

Apologies

Jennifer Martin
Marius Rademaker (Deputy Chair)

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. Apalutamide for the treatment of high-risk, non-metastatic, castration-resistant prostate cancer (HR nmCRPC)

Application

2.1. The Committee reviewed correspondence and new information provided by the supplier (Janssen), regarding its funding application for apalutamide for high-risk, nonmetastatic, castration-resistant prostate cancer (nmCRPC).

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 reiterated its previous **recommendation** that the application for apalutamide be deferred.

2.3.1. In reiterating this recommendation, the Committee noted that, although a health benefit of apalutamide was reported in terms of overall survival in the SPARTAN trial, 1) the Committee had reservations about the validity of the estimate of overall survival in that trial, 2) that there was an ongoing lack of reported evidence for quality of life improvement with apalutamide, and 3) that no additional health-related quality of life data was provided for assessment by the Committee.

2.3.2. The Committee considered that specialised advice from CaTSoP remained important to inform further assessment of this application; reiterated its February 2020 requests for specific advice; and considered that this advice should be in the setting of emerging evidence for other similar agents for this indication (daralutamide and enzalutamide), in particular whether the health effects could be considered a class effect.

Discussion

2.4. The Committee noted that, in February 2020, PTAC reviewed the application for apalutamide (Erlyand) for the treatment of high-risk, nonmetastatic, castration-resistant prostate cancer (HR nmCRPC). At that time, the Committee:

2.4.1. Recommended that the application for apalutamide for high-risk, nonmetastatic, castration-resistant prostate cancer (nmCRPC) be deferred, due to the lack of a statistically significant change in overall survival (OS), which the Committee considered to be the primary potential benefit of apalutamide, and no reported evidence for quality of life improvement with apalutamide; and

2.4.2. Requested advice from the Cancer Treatments Subcommittee (CaTSoP) regarding: the appropriate timing for its review of this application; likely patient numbers; the impact apalutamide may have on subsequent abiraterone use for patients with metastatic disease; the health need for another agent for high risk nmCRPC in a New Zealand setting; any evidence to support optimal sequencing of this class of agents and abiraterone; the value of metastasis-free survival (MFS) as a surrogate for OS in high risk nmCRPC with supporting evidence for this; views on the proposed Special Authority criteria; and whether there is a class effect from use of these agents.

2.5. The Committee noted the supplier's response to the February 2020 PTAC record, which included conference presentation slides regarding the final overall survival (OS) analysis of the SPARTAN clinical trial data and publication of the final SPARTAN OS data (Smith MR, et al. Apalutamide and Overall Survival in Prostate Cancer. Eur Urol. 2020:S0302-2838(20)30628-X, https://doi.org/10.1016/j.eururo.2020.08.011]).

2.6. The Committee noted that OS was a pre-specified secondary outcome of the SPARTAN trial, and testing of OS was based on a prespecified O'Brien-Fleming-type alpha-spending function. The Committee noted that after median follow-up of 50.4 months, the final OS data from SPARTAN reported a hazard ratio (HR) for death of 0.78 with apalutamide compared with placebo (95% CI: 0.64 to 0.96; *P*= 0.016) in the intention-

to-treat population, with the P value crossing the prespecified O'Brien-Fleming boundary of 0.046 and upper limit of the 95% confidence interval approaching 1.

2.7. The Committee noted that 84% of patients who received placebo in SPARTAN crossed over to receive apalutamide or other active therapy, and that the first subsequent therapy received by about three-quarters of patients in the apalutamide and placebo groups, respectively, was abiraterone acetate with prednisone. The Committee noted the two exploratory OS sensitivity analyses' results after adjustment for patient crossover from placebo to apalutamide [HR 0.69 (95% CI: 0.56 to 0.84); nominal *P* = 0.0002] and considered these results were consistent with patients who received abiraterone post-apalutamide not being disadvantaged in terms of overall survival outcome. Members considered that, for cost-effectiveness modelling purposes, the hazard ratio for OS after adjustment for crossover could be representative of clinical benefit from apalutamide in New Zealand, and considered this could inform subsequent analysis using appropriate sensitivity analyses.

2.8. The Committee considered that, overall, its interpretation of the benefit of apalutamide from the OS data was limited by reservations and a lack of clarity regarding adjustments for the multiple sequential SPARTAN trial statistical analyses. This included:

2.8.1. Members could not replicate the P values for adjustment for multiple looks at the data and the O'Brien-Fleming based alpha bounds were likely overspent during the multiple analyses, consequently the P value was likely too precise, and that the confidence intervals were consequently likely wider than reported (with appropriate alpha-levels for multiple measurement requiring confidence limits beyond 95%).

2.8.2. Members noted that OS for this study was a secondary outcome (one of many), so even with an adjustment for repeated measurements within a variable with sequential analysis, there would still be unaccounted type I error inflation. Members considered that even if the concept of correcting for type I error for repeated measurement was adhered to, the principle of controlling overall experiment-wide error had not been, and there was therefore possible reporting bias.

2.8.3. Members noted the upper 95% confidence limit of 0.96 for the final OS HR was close to the null, so that even if OS was a primary outcome the evidence against the null hypothesis of no survival difference (ignoring cross-over) might arguably be regarded as only moderate; and would be even closer to the null if the correct alpha-related confidence bounds had been used.

2.9. The Committee noted the supplier's response regarding the health-related quality of life (HRQOL) data for the SPARTAN trial, which stated that there was no difference between treatment groups. However, the Committee considered that the data provided was insufficient to inform a full assessment by the Committee of HRQOL that could be attributed to apalutamide treatment.

2.10. Members noted that OS data have recently been reported for phase III clinical trials of darolutamide (ARAMIS trial) and enzalutamide (PROSPER trial) in patients with non-metastatic castration-resistant prostate cancer, and considered that there may be a class effect for androgen-receptor inhibitors in this setting. Members considered there may be some pharmacological differences between agents, including binding properties in the presence of androgen receptor mutations. The Committee considered that the evolving evidence for two more agents in the androgen-receptor inhibitor class would likely change the context of the assessment of apalutamide in this setting.

2.11. The Committee noted that advice from CaTSoP had not yet been sought regarding the application for apalutamide, and considered that such expert advice was required to

inform an assessment. In addition, the Committee considered that CaTSoP could provide advice regarding apalutamide in the context of the new evidence for darolutamide and enzalutamide.

2.12. The Committee noted that its February request for advice about metastasis-free survival (MFS) was less relevant now, in the setting of provision of estimates of OS.

2.13. Overall, the Committee considered the amount of benefit of apalutamide was unclear from the OS data provided due to reservations about the validity of the statistical analyses, and considered that the HRQOL impact of apalutamide could not be determined from the data provided. The Committee considered that this new data was insufficient to change its original recommendation to defer the application, without further advice from CaTSoP. The Committee reiterated its recommendation to defer the application, and considered that CaTSoP's advice would be required to further inform assessment of the application, noting the recent evidence for other agents in this setting.

3. Zonisamide - severe refractory epilepsy

Application

3.1. The Committee reviewed the application for zonisamide in the treatment of epilepsy.

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

Recommendations

3.3. The Committee recommended that zonisamide be listed with a low priority as monotherapy for the treatment of refractory partial epilepsy.

3.4. The Committee recommended that zonisamide be listed with a high priority as an adjunctive treatment for refractory partial epilepsy.

3.5. The Committee recommended that zonisamide be listed with a high priority for the treatment of severe childhood epilepsy syndromes, including Lennox-Gastaut Syndrome (LGS) and similar epileptic encephalopathies.

3.6. In making its recommendations, the Committee considered that there was the greatest evidence of benefit for zonisamide as an adjunctive treatment, and that severe childhood epilepsy syndromes carried a particularly high health need and that this informed the relative priority rankings of the three recommended groups.

Discussion

3.7. The Committee noted that epilepsy is a group of neurological disorders characterised by epileptic seizures. The Committee noted that the manifestations of seizures usually involves involuntary motor activity of variable durations and severity with or without alterations in the level of consciousness. Some seizure types are primarily associated with altered levels of consciousness. The Committee noted that epilepsy is a chronic condition, and that lack of adequate control can have important consequences, including injury with seizure, an inability to drive or work in certain occupations, affects education, and results in reduced quality of life. The Committee noted that epilepsy is associated with unexpected death.

3.8. The Committee noted estimates that 45,000 to 50,000 New Zealanders have epilepsy, with 2000 new diagnoses each year (Ministry of Health, 2019). The Committee noted that Māori patients have worse outcomes compared with non-Māori with epilepsy in New

Zealand (Bergin et al. Epilepsia. 2019;60:1552-64; Hamilton et al. Epilepsia. 2020;61:519-29).

3.9. The Committee noted that patients whose seizures do not successfully respond to three anti-epilepsy drugs of sufficient treatment length are considered to have treatment-refractory epilepsy, and that 20-40% of patients with epilepsy are estimated to fulfil this criterion. The Committee noted that the health need of people with treatment-refractory epilepsy is significant and that these people have the greatest burden of epilepsy-related disabilities. The Committee also considered that treatment-refractory epilepsy has a significant impact on family and whānau, particularly in regard to managing seizures and potential educational or employment loss.

3.10. The Committee noted that PHARMAC currently funds 16 anti-epilepsy medicines in the Anti-Epilepsy Therapeutic Group, 13 of which are funded without restriction. The Committee noted that the currently available treatments have a wide variety of side effects. The Committee considered that the current treatment paradigm for anti-epilepsy treatment appears is related both to the type of epilepsy and clinician judgement of individual patient needs. The Committee considered that it is unclear exactly where zonisamide would sit within this paradigm.

3.11. The Committee noted that zonisamide is an oral sulfonamide derivative that is chemically and structurally unrelated to other anticonvulsants. The Committee noted that it is not entirely clear how it produces its anti-epilepsy effect; however it acts to block both voltage-dependent sodium and T-type calcium channels, disrupting synchronised neuronal firing and reducing the spread of abnormal electrical activity in the brain, thus likely disrupting subsequent epileptic activity. The Committee noted that zonisamide also has a modulatory effect on gamma-aminobutyric acid (GABA)-mediated neuronal inhibition.

3.12. The Committee noted that there is currently no Medsafe approved zonisamide product available in New Zealand.

3.13. The Committee noted the results of a phase III, randomised, double-blind, parallel-group, non-inferiority trial that investigated the use of zonisamide compared with carbamazepine in adults with newly diagnosed partial epilepsy (Baulac et al. Lancet Neurol. 2012;11:579-88). The Committee noted that 79.4% in the zonisamide group and 83.7% carbamazepine group were seizure-free for 26 weeks (adjusted absolute treatment difference -4.5%; 95% confidence interval (CI) -12.2 to 3.1%), while 67.6% zonisamide group and 74.7% of the carbamazepine group were seizure-free for 52 weeks (adjusted absolute treatment difference -7.9%; 95%CI -17.2 to 1.5%). The Committee considered that the study was reasonably designed and adequately powered.

3.14. The Committee also noted the results of the following randomised, double-blind, placebo-controlled trials of zonisamide as an adjunctive treatment:

3.14.1. A study of people aged ≥12 years with partial seizures, unsatisfactorily controlled despite a stable regimen of one to three AEDs, treated with 100 mg, 300 mg or 500 mg zonisamide or placebo (n=351) (Brodie et al. Epilepsia. 2005;46:31-41). The Committee noted that a ≥50% decrease from baseline in seizure frequency (response rate) was experienced in 52.3% of the 500 mg zonisamide group, compared with 21.3% placebo (OR 4.07; 95% CI: 1.94-8.56). The Committee considered that study was adequately powered.

3.14.2. A study of people aged ≥12 years of age with refractory partial-onset seizures, concomitantly taking one or two other anti-epilepsy drugs, treated with 400 mg zonisamide or placebo (n=230) (Faught et al. Neurology. 2001;57:1774-9. The Committee noted that the percentage of patients with a ≥50% reduction in

seizure frequency from baseline (response rate) was 43% in the zonisamide group compared with 22% placebo (p=0.014).

3.14.3. A study of people aged 6-17 years with a clinical diagnosis of epilepsy with partial onset seizures, concomitantly taking one or two other anti-epilepsy drugs, treated with zonisamide (maximum dose 500 mg) or placebo (n=207) (Guerrini et al. Epilepsia. 2013:54:1473-80). The Committee noted that a ≥50% seizure frequency reduction from baseline was experienced by 50% of the zonisamide group compared with 31% placebo (p=0.0044).

3.14.4. A study of people with refractory partial-onset epilepsy concomitantly taking one or two other anti-epilepsy drugs, treated with 300 mg or 400 mg zonisamide or placebo (n=104) (Lu et al. Clin Drug Investig. 2001;31:221-9). The Committee noted that the percentage of patients with a ≥50% reduction in seizure frequency from baseline (response rate) was 55.2% in the 300 mg zonisamide group, 56.5% in the 400 mg zonisamide group and 36.0% in placebo (p<0.05), with no significant difference observed between the 300 mg and 400 mg groups. The Committee noted there was no reported difference in adverse events between groups.

3.14.5. A study of people aged 16-65 years with a history of partial seizures refractory to at least one concomitant anti-epilepsy drug, treated with 400-660 mg zonisamide or placebo (n=152) (Sackrllares et al. Epilepsia. 2004;45:610-7). The Committee noted that the percentage of patients with a ≥50% reduction in seizure frequency from baseline (response rate) was not statistically significant between groups.

3.14.6. A study of people aged 19-59 years with complex partial seizures, concomitantly taking up to three other anti-epilepsy drugs, treated with up to 20 mg/kg/day zonisamide or placebo (Schmidt et al. Epilepsy Res. 1993. 15:67-73). The Committee noted that the percentage of patients with a ≥50% reduction in seizure frequency from baseline (response rate) was 29.9% in the zonisamide group compared with 9.4% placebo (p<0.05). The Committee noted that this study used a relatively low dose of zonisamide and given this, questioned the study's relevance.

3.15. The Committee noted the results of the following retrospective cohort studies that investigated the use of zonisamide in children with childhood epilepsy syndromes:

3.15.1. Children with intractable epilepsy (including a subset with Lennox Gastaut Syndrome (LGS)) whose seizures were not controlled by two or more conventional anti-epilepsy drugs and were treated with zonisamide as an adjunctive treatment (n=163) (Lee et al. Brain and Devel. 2010;32:208-12). The Committee noted 48.5% of children had a 50% or greater reduction in seizure frequency and 15.3% became seizure free. The Committee noted all adverse events were mild.

3.15.2. Children with LGS whose seizures were not controlled by a combination of two or more anti-epilepsy drugs (n=62), mean follow up 52.4 months (You et al. Brain Dev. 2008;30:287-90). The Committee noted that 4.8% participants experienced 100% seizure control, 22.6% experienced 75-100% reduction in seizure frequency, and 24.2% experience 50-75% reduction in seizure frequency.

3.16. The Committee noted the results of the Cochrane meta-analysis of zonisamide as monotherapy compared with carbamazepine (Nevitt et al. Cochrane. 2017;6:CD011412). The Committee noted that zonisamide demonstrated non-inferiority

to carbamazepine for time to withdrawal of treatment, time to six- and 12-month remission, and time to first seizure.

3.17. The Committee noted the results of an indirect comparison network meta-analysis of the efficacy and tolerability of anti-epilepsy drugs in refractory epilepsy (Zhuo et al. Sci Rep. 2017;7:2535). The Committee noted that for 50% responder rate, zonisamide was non-inferior to a number of anti-epilepsy drugs including lamotrigine, levetiracetam, gabapentin, and pregabalin. The Committee also noted that zonisamide reported non-inferiority to placebo and a number of anti-epilepsy drugs for dizziness and somnolence adverse events.

3.18. The Committee considered that overall, the evidence for zonisamide in epilepsy was of moderate to good strength and quality; noting that there were a number of relevant trials, studies and analyses, although most of these were for adjunctive treatment in adults. The Committee considered that zonisamide would likely, through reducing seizures, produce health benefit for not only the patient, but also for family, whānau and wider society by reducing family burden of care, depression and anxiety, and may improve ability to work.

3.19. The Committee noted that the applicant proposed that if Special Authority criteria were required, that criteria similar to lacosamide may be appropriate. The Committee noted that this would place zonisamide as a sixth-line treatment option. The Committee considered that, with advancing more refractory disease, the later in the treatment paradigm an epilepsy medicine is, the less efficacious it is likely to be for people with refractory epilepsy, and therefore considered that it would be preferable for zonisamide to be an available option earlier than sixth line. The Committee acknowledged that zonisamide may be more expensive than alternative anti-epilepsy drugs, and that any funding criteria implemented would likely be for fiscal management. The Committee considered that any Special Authority criteria for zonisamide should be on the advice of a specialist neurologist, general physician or paediatrician.

3.20. The Committee considered that this proposal would not clearly result in any substantial additional costs or savings to the health system. Members considered that if zonisamide were to reduce the number of seizures, even if less than the 50% seizure reduction used in clinical trials as the key outcome measured, particularly in children, the clinical impacts would be considerable including reduction in seizure-related hospitalisations. This may reduce hospital related costs. Members considered the needs, especially of children with treatment-resistant severe frequent seizures, to be very high, with any appreciable decrease in seizure frequency or severity having major benefits for patients and their caregivers/family/whānau.

3.21. The Committee considered that if zonisamide were listed on the Pharmaceutical Schedule that more patients would likely be treated with zonisamide, compared to those currently receiving zonisamide through the NPPA pathway.

3.22. The Committee considered that for the purposes of either economic modelling or consideration of individuals with exceptional refractory disease under the Named Patient Pharmaceutical Assessment (NPPA) scheme, regardless of treatment (either zonisamide or any other epilepsy treatments), PHARMAC staff could seek advice from the Neurological Subcommittee regarding baseline seizure rates in these patient groups in New Zealand (noting the large variability on this in the literature) in order to assess the appropriateness of a 50% reduction in seizures and whether lesser reductions could still provide clinically meaningful improvements for these patients with very high need. The Committee also considered it would be useful to seek the Neurological Subcommittee's advice on the total number of patients who would be expected to use zonisamide and which pharmaceuticals zonisamide would be used in combination with.

4. Zoledronic acid - preventing bone loss post spinal cord injury

Application

4.1. The Committee reviewed the application for zoledronic acid for prevention of bone loss following spinal cord injury.

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

Recommendation

4.3. The Committee recommended that access to zoledronic acid be widened for the prevention of bone loss following spinal cord injury with a high priority subject to the following Special Authority criteria:

Initial application — (spinal cord injury) from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Patient has experienced an acute traumatic spinal cord injury in the last six months; and
2. Patient is being managed in a specialist spinal acute care and rehabilitation unit; and
3. Patient is contraindicated to, or has trialled and is unable to tolerate, oral bisphosphonate therapy; and
4. The patient will not be prescribed more than 5 mg of zoledronic acid in a 12-month period.

Renewal – (prevention of bone loss following spinal cord injury) from any relevant practitioner.

1. The patient remains unable to tolerate oral bisphosphonate therapy; and
2. The patient will not be prescribed more than 5 mg of zoledronic acid in a 12-month period.
3. The patient has not received two or more doses of zoledronic acid for this indication

4.4. In making this recommendation, the Committee considered the high health need of patients who experience bone loss following spinal cord injury (SCI), noting the increased risk of bone fracture, the evidence supporting a reduction in loss of bone mineral density (BMD) following treatment with zoledronic acid, higher prevalence of SCIs in Māori and Pasifika, and the suitability of zoledronic acid treatment compared to current oral treatments.

Discussion

4.5. The Committee noted the Clinician application for the use of zoledronic acid in the treatment of bone loss for patients following SCI, noting SCI to be devastating with the possibility of lifetime disability. The Committee noted that SCI is associated with a rapid and profound loss of BMD of approximately 1% per week for 6-12 months post-injury, compared to other osteoporotic states. The Committee considered that the rate of reduction in BMD generally plateaus 24 months following injury.

4.6. The Committee noted that low BMD levels are a contributor to the incidence of low trauma fractures in osteoporotic states. The Committee noted the associated complications and difficulties in treating fractures in individuals with a SCI such as altered fracture healing, delayed union, malunion and non-union, pressure sores, infection, and osteomyelitis, which may result in prolonged immobilisation and hospitalisation that may negatively impact quality of life (Giangregorio et al. J Spinal Cord Med. 2006;29:489-500).

4.7. The Committee considered that the aetiology of BMD loss following SCI is unclear, however many factors may have an impact including; loss of neuronal stimuli, catabolic state, altered anabolic milieu, and early high dose steroid treatment in the SCI treatment algorithm. The Committee noted that trabecular bone is generally affected more than cortical bone, and that femur and tibia (sub-lesional) sites often experience the most profound reductions in BMD.

4.8. The Committee noted that Māori and Pacific have higher age-adjusted incidence rates for spinal cord injuries compared with NZ European (Derrett et al. Inj Prevent. 2012;18:343-6).

4.9. The Committee noted a retrospective cohort analysis 8,150 veterans with chronic multiple sclerosis (MS, n=1,789) or traumatic SCI (n=6,361), which reported a mean per-person fracture rate of 3.1 per 100 patient-years (Logan et al. Arch Phys Med Rehabil 2008:89: 237-43). The Committee also noted a higher risk of fracture in those with some motor impairment (RR=2.33, p<0.001). The Committee considered that this analysis had limitations due to the inclusion of patients with MS.

4.10. The Committee noted a retrospective 10-year follow-up study of 63 patients with recent SCI, which reported fractures were observed 6.4 ± 2.4 years after SCI (Gifre et al. Clin Rehabil 2014: 28: 361-9). The Committee noted that 50% of patients presented with associated clinical complications, and that severity of SCI was a risk factor associated with the development of fractures.

4.11. The Committee noted a retrospective chart review of 325 individuals with SCI and osteoporosis-related fractures, which reported a mean time between SCI and fracture was 9.7 (standard deviation ± 9.3) years (Champs et al. Spinal Cord 2020: 58: 484-9). The Committee noted that 82% of fractures occurred in lower limbs (distal femur, 27%; proximal femur, 27%; tibia and/or distal fibula, 28%).

4.12. The Committee noted that zoledronic acid is an intravenous bisphosphonate treatment that acts as an inhibitor of osteoclast-mediated bone resorption and is currently funded for a number of indications, including osteoporosis, subject to Special Authority. The Committee noted that zoledronic acid is not approved for use in patients with significant baseline renal impairment (creatinine clearance <35 ml/min). The Committee considered that the safety profile of zoledronic acid is well described in clinical trials of patients with osteoporosis, with 6% of patients treated with zoledronic acid experiencing infusion-site reactions and 20-30% experiencing transient influenza-life symptoms shortly after treatment.

4.13. The Committee noted that oral bisphosphonate treatments carry the risk of oesophagitis and as a result, patients must remain upright after an oral dose for 30 minutes. The Committee considered that such postural requirements were usually not possible in the acute spinal cord injury setting, and that such patients, or patients who are otherwise contraindicated to these treatments, currently do not receive bisphosphonate treatment of any sort for the prevention of bone loss immediately following SCI beyond supportive care.

4.14. The Committee considered that, in the context of this application, the patient population who would most benefit from zoledronic acid would be those contraindicated to or unsuited for oral bisphosphonates, with severe SCI, being treated in a rehabilitation unit. Members considered that people with non-traumatic spinal cord injuries (e.g. degenerative) are often eligible for zoledronic acid treatment through other Special Authority criteria.

4.15. The Committee noted 2018 data from two supra-regional SCI sites, which reported 217 new patients with SCI cases in people aged 16 to 95 years discharged with tetraplegia or paraplegia (New Zealand Spinal Cord Injury Registry, 2018). The Committee noted that 45.8% of patients had an American Spinal Injury Association impairment scale grade of A, B or C at discharge, and that the rehabilitation length of stay typically varied between 55-65 days.

4.16. The Committee considered that earlier administration of bisphosphonate therapy after SCI would be expected to confer the greatest benefit in reducing loss of BMD, and that patients would likely be in hospital at the time treatment would be administered. The

Committee therefore considered approximately 100% of eligible patients would be treated with zoledronic acid shortly following a SCI; however, only 30-40% of patients would likely require re-treatment with 12 months as many patients would have sufficiently recovered to be able to sit up and thus likely to be able to tolerate oral bisphosphonates, and would therefore not meet the renewal criteria.

4.17. The Committee noted the results of the following randomised, double-blind, placebo-controlled trials of the use of zoledronic acid to prevent bone loss following SCI:

4.17.1. A study of patients with spinal cord injury and neurological deficits sustained within 3 months of study initiation (Goenka et al. Spinal Cord. 2018;56:1207-11). The Committee noted that after one year the mean bone mineral density difference at the femoral neck was 0.806 g/cm^2 in the zoledronic acid group compared with 0.729 g/cm^2 (p=0.003) in placebo and at the total hip was 0.845 g/cm^2 vs 0.734 g/cm^2 (p<0.001).

4.17.2. A study of adult patients with C4-T10 complete traumatic spinal cord injuries (n=15), one year follow up (Oleson et al. Spinal Cord. 2020; DOI 10.1038/s41393-020-0431-9). The Committee noted after one year, the mean difference between percentage change of bone mineral density between zoledronic acid and placebo were: total proximal femur: 13.1 (p=0.002), intertrochanteric femur: 10.8 (p=0.004), femoral neck: 13.1 (p=0.013), distal femur: 1.94 (p=0.622), and proximal tibia: 5.49 (p=0.421).

4.17.3. A study of patients who had experienced a spinal cord injury in the previous six months (n=16) (Schnitzer et al. PM R. 2016;8:833-43). The Committee noted at six months there were statistically significant smaller reductions in bone mineral density at the hip and femoral neck for the group treated with zoledronic acid compared with the placebo group (mean difference in percentage change in BMD between zoledronic acid and placebo group at right hip: 6.4 (p=0.03); left hip: 8.6 (p=0.03); right femoral neck: 14.9 (p=0.01); left femoral neck: 10.0 (p=0.02)).

4.17.4. A study of patients with acute traumatic C2 to T12 spinal cord injury (Shapiro et al. Calcif Tissue Int. 2007;80:316-22). The Committee noted after one year, patients treated with zoledronic acid experienced statistically significant smaller reductions in bone mineral density at the narrow-neck and shaft of the femur compared to placebo.

4.18. The Committee also noted the results of the following cohort studies of zoledronic use following spinal cord injury:

- Bauman et al. J Bone Miner Metab. 2015;33:410-21
- Bubbear et al. Osteoporosis Int. 2011;22:271-9

4.19. The Committee noted the results of the systematic review and meta-analysis by Chang et al, which examined the use of bisphosphonates following spinal cord injury to attenuate sub-lesional bone loss (Chang et al. PLoS One. 2013;8:e81124).

4.20. The Committee considered there was evidence that zoledronic acid reduced the loss of BMD; however, noted it did not identify any direct evidence on the impact of zoledronic acid use on bone fracture after acute SCI. The Committee considered that in the absence of this, it was reasonable to assume that a reduction in the loss of BMD would reduce fracture rate in these patients. The Committee also considered that the evidence of zoledronic acid in reducing BMD loss and reducing fracture risk in osteoporosis was of good strength and quality; noting that these trials often recruit participants with low BMD, the Committee considered that it is reasonable to assume zoledronic acid has a similar effect in the acute SCI setting.

4.21. The Committee considered that all people being treated with bisphosphonates should also receive colecalciferol, noting that a combination oral alendronate and colecalciferol product is currently funded; therefore, people who receive zoledronic acid for SCI may also receive oral colecalciferol supplementation. The Committee considered that patients may also undergo dental assessment due to the risks of osteonecrosis of the jaw associated with bisphosphonate treatment.

4.22. The Committee noted that a single dose of zoledronic acid via intravenous infusion is generally not difficult to administer and, given relative infrequency (once a year), considered that zoledronic acid would likely be more suitable for many patients compared with once-weekly oral bisphosphonates. The Committee considered that there would likely be minimal impact to the health system from this proposal, as zoledronic acid is infused over a short time period and many of the recipients would be in pre-rehabilitation or rehabilitation care in hospital when they receive the initial infusion.

4.23. The Committee noted that there may be barrier to access for subsequent infusions of zoledronic acid for patients with SCI, noting there is often costs associated and access for these patients can be difficult. However, the Committee considered that a significant proportion of patients would not require follow-up zoledronic acid intravenous infusion in the community, as they would be able to tolerate oral treatment given improvements in their ability to be upright.

5. Diflunisal for transthyretin amyloidosis (ATTR) cardiomyopathy

Application

5.1. The Committee reviewed two consumer applications for diflunisal for the treatment of transthyretin amyloidosis (ATTR) cardiomyopathy. The Committee noted that one of the consumer applications was from a representative of the New Zealand Amyloidosis Patients Association (NZAPA) for ATTR cardiomyopathy in general i.e. both hereditary mutated and wild-type; the other was from a patient with ATTR wild-type (ATTRwt) cardiomyopathy who requested diflunisal be considered specifically for ATTRwt cardiomyopathy.

5.2. The Committee noted that PHARMAC sought advice from the Committee regarding both ATTRwt cardiomyopathy and the hereditary mutated form of the disease, ATTRm cardiomyopathy.

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

Recommendation

5.4. The Committee recommended that diflunisal be funded with a low priority subject to the following Special Authority criteria:

DIFLUNISAL
Special Authority for Subsidy
Initial application from a haematologist, cardiologist or relevant medical specialist on the recommendation of a haematologist or cardiologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient has mutated or wild-type ATTR (transthyretin) amyloidosis; and
2 Patient has histological confirmation of ATTR based on cardiac or non-cardiac biopsy; and
3 Patient's symptoms meet the criteria of the New York Heart Association (NYHA) Class I, II or III.

Renewal – from any relevant practitioner on the recommendation of a haematologist, cardiologist or relevant medical specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. The treatment remains appropriate and the patient is benefiting from treatment; and
2. Patient's symptoms meet the criteria of the New York Heart Association (NYHA) Class I, II or III.

5.5. In making this recommendation, the Committee considered: the high health need of this patient group; the lack of a funded disease-modifying treatment; a possible survival benefit with diflunisal compared to best supportive care in ATTR cardiomyopathy, based on low quality evidence i.e. retrospective case-control studies with small patient numbers, and inherent differences between patient groups at baseline; the well-established NSAID safety profile of diflunisal; and the suitability of an oral treatment, noting that there is currently no Medsafe-approved diflunisal product for any indication.

Discussion

5.6. The Committee noted that amyloidosis is a group of diseases in which a pathologically abnormal protein causes amyloid (fibril) deposits to accumulate in organs, leading to rapid and progressive damage. The Committee noted that abnormal transthyretin (TTR) protein which is produced in the liver causes transthyretin amyloidosis (ATTR), which arises from either mutated TTR (ATTRm) or wild-type TTR (ATTRwt) and can result in cardiomyopathy and heart failure due to amyloid deposits accumulating in the heart.

5.7. The Committee considered that patients with amyloidosis have a high health need due to the severe and chronic nature of the disease and noted that the average overall survival is approximately three to five years from diagnosis. The Committee noted that many patients have moderate to severe symptomatic cardiomyopathy corresponding to New York Heart Association (NYHA) functional classification of III or IV at diagnosis, and that a UK study reported diagnoses of ATTR cardiomyopathy occurring three to four years after presentation with cardiac symptoms, during which time many patients used hospital services (Lane et al. Circulation. 2019;140:16-26).

5.8. Members noted that, in addition to heart failure, progressive neuropathy is a substantial issue for many people with ATTR (Kapoor et al. J Neuromuscul Dis. 2019;6:189-99), however, members considered that biological differences may exist between the disease of patients with ATTR with neuropathy compared with those without neuropathy.

5.9. The Committee noted that patients with ATTRwt cardiomyopathy typically present between 60 to 70 years of age, possibly accompanied or preceded by carpal tunnel syndrome, whereas earlier presentation is likely with ATTRm cardiomyopathy, occurring from about thirty years of age and onward. The Committee noted that there is currently no data to indicate whether ATTR cardiomyopathy disproportionately affects Māori, Pacific people or groups experiencing health disparities.

5.10. The Committee noted that while the true prevalence (estimated in a Japanese hospital database cross-sectional study to be 70-86 cases of ATTRwt per million and 2.4-2.9 cases of ATTRm per million) may be underestimated, there is evidence that the prevalence and incidence of ATTR cardiomyopathy (and ATTRwt in particular) is increasing worldwide (Winburn et al. Cardiol Ther. 2019;8:297-316; Gilstrap et al. Circ Heart Fail. 2019;12:e005407; Lane et al. Circulation. 2019;140:16-26). This is likely a result of increased awareness, diagnosis (including non-invasive imaging), and treatment options. Members considered that the prevalence of mutated disease in New Zealand is lower than previously estimated, with approximately 30 patients who have ATTRm cardiomyopathy seen per year.

5.11. The Committee noted that there are no funded disease-modifying treatments for ATTR cardiomyopathy in New Zealand. Unfunded treatments which are being used or investigated internationally for ATTR cardiomyopathy aim to either suppress TTR e.g. inotersen, patisiran, stabilise TTR e.g. tafamidis, or disrupt or reabsorb TTR e.g. monoclonal antibodies.

5.12. The Committee noted that liver transplant (or combined liver and heart transplant) are treatment options in New Zealand for some patients with ATTR cardiomyopathy. These are undertaken to suppress production of abnormal TTR in the liver, however, transplant

may not be suitable for all patients and may not be curative because amyloid can continue to accumulate even after transplantation.

5.13. The Committee noted that, in May 2019 the Cardiovascular Subcommittee considered a proposal for the funding of tafamidis for the treatment of cardiac amyloidosis that is specifically caused by transthyretin amyloidosis (ATTR); including both ATTRm and ATTRwt. The Cardiovascular Subcommittee recommended tafamidis be funded with a medium priority, subject to restrictions under Special Authority. In making this recommendation, the Subcommittee noted the high health need of patients and lack of funded pharmaceutical treatments that modify disease progression.

5.13.1. Patient characteristics in the Special Authority restrictions for tafamidis recommended by the Cardiovascular Subcommittee included ATTR cardiomyopathy (either hereditary mutated or wild-type) with no/minimal or mild symptoms of heart failure i.e. NYHA class I and II.

5.13.2. In August 2019, PTAC reviewed the Cardiovascular Subcommittee's record, noted a survival benefit associated with tafamidis and recommended that it review the application for tafamidis, based on the likely high cost of this medicine, once there was a clear signal that a product would be registered in New Zealand.

5.13.3. In September 2019, the Rare Disorders Subcommittee reviewed the Cardiovascular Subcommittee's record regarding tafamidis and considered there was uncertainty in patient numbers but that it was likely at least 100 people in New Zealand would have this condition, and that rates of diagnosis were likely to increase in future.

5.13.4. The Committee noted that tafamidis is under assessment by PHARMAC and staff have contacted the supplier (Pfizer), however, there has been no formal response regarding regulatory approval or supply of tafamidis in New Zealand.

5.14. The Committee noted that diflunisal is a long-established non-selective non-steroidal anti-inflammatory drug (NSAID) that the Committee understood was approved for use in New Zealand from the late 1970s until 1999. The Committee noted that, based on *in vitro* and phase I clinical trial evidence, diflunisal stabilises TTR tetramers through its interaction with TTR's thyroxine binding site, and has been proposed as a disease-modifying pharmaceutical for ATTR cardiomyopathy.

5.15. The Committee noted that diflunisal is a tablet that is taken orally every 8 to 12 hours, swallowed whole, at around the same time each day at a dose of 250 mg twice daily for ATTR cardiomyopathy. The Committee considered that, as an oral formulation, diflunisal would be suitable for long-term treatment, noting that tablet splitting may be required if a 500 mg tablet were funded.

5.16. The Committee noted that NSAIDs carry risks in relation to gastrointestinal bleeding, and considered that the risk associated with diflunisal would be moderate relative to other NSAIDs. Members noted that a six-month study in patients with osteoarthritis reported fewer side effects (including gastrointestinal effects) with diflunisal compared with ibuprofen or acetylsalicylic acid (Andrew et al. Br J Clin Pharmacol. 1977;4(Suppl 1):45S-52S). The Committee considered it was reasonable to expect the general safety profile of diflunisal to be similar to that of other non-selective NSAIDs as a result of a likely class effect of NSAIDs. The Committee considered that, as with much non-selective NSAID prescribing, diflunisal would likely be used in combination with a proton pump inhibitor and/or an H2 antagonist. The Committee also noted that, in line with NZ Formulary guidance, NSAIDs should be used with caution in patients with cardiac impairment, and should be avoided if possible or used with caution in patients with renal impairment.

5.17. The Committee noted that there is currently no diflunisal product approved by Medsafe, and that the approval of two previously approved diflunisal products has lapsed. The Committee noted that diflunisal is approved by the FDA (USA) and EMA (Europe) for use in indications such as pain relief, inflammation and rheumatoid arthritis; that in Australia diflunisal can be accessed for the treatment of amyloidosis via the Special Access Scheme; and that it appears to be used off-label in other countries for the treatment of ATTR cardiomyopathy.

5.18. The Committee considered it unlikely that a supplier would seek Medsafe approval of diflunisal for the treatment of ATTR cardiomyopathy, given relatively small patient numbers and the apparent absence of approval in any international jurisdiction. The Committee considered that, while it would be preferable to fund an approved product, the funded use of diflunisal in New Zealand without Medsafe approval i.e. accessed via Section 29 of the Medicines Act, would be reasonable, given that diflunisal has previously been approved by Medsafe, the known NSAID safety profile of diflunisal, and its international off-label use in this indication.

5.19. The Committee noted that the evidence base for the efficacy of diflunisal for ATTR cardiomyopathy consists of low-quality non-experimental evidence from retrospective case control studies, with no phase III randomised controlled trials identified in patients with ATTR cardiomyopathy.

5.20. The Committee noted the results from a retrospective, case-control single-centre cohort study in 120 patients with ATTR cardiac amyloidosis presenting to a US specialist centre between 2001 and 2016 who either received a stabiliser (N = 29; either diflunisal [N = 13] or tafamidis [N = 16]) or did not receive a stabiliser (N = 91) and who were followed up for a median of 1.9 years (Rosenblum et al. Circ Heart Fail. 2018;11:e004769). The Committee noted that patients who received stabilisers were NYHA class I (N = 2), class II (N = 21) or class III (N = 6); none were NYHA class IV.

5.20.1. The Committee noted that there were differences between groups at baseline including the proportion of ATTRm patients in each group, NYHA severity and renal function. The Committee considered that patients who received a stabiliser likely had a less severe disease phenotype at baseline compared with patients who did not receive a stabiliser, and considered this potential selection bias affected the quality of the evidence.

5.20.2. The Committee noted that the risk of the combined endpoint of death or orthotopic heart transplant (OHT) was lower with stabiliser use compared with no stabiliser use (hazard ratio (HR) 0.32, 95% CI 0.18 to 0.58, P<0.0001) and that the findings persisted after adjustment for all non-linear covariate predictors. The Committee considered that this statistically significant result may have been confounded by the case control data used for analysis.

5.20.3. The Committee noted that the authors reported survival probability for each of the two stabiliser types separately, compared with no stabiliser use, and considered that these results indicated a similar benefit over time between the two stabilisers, although limited by very small patient numbers contributing data to the later years of follow-up and the various between-group differences in disease severity at baseline. The Committee considered that the evidence comparing stabiliser type was hypothesis-generating and limited by the small sample size.

5.21. The Committee noted the results from a retrospective study of 105 patients with ATTRwt cardiac amyloidosis seen between 2009 and 2016 who were treated with diflunisal for at least one year (N = 35), or untreated (N = 70), which were published in abstract form only (Mints et al. Circulation. 2019;140 [Suppl_1]: Abstract Nr. 13123).

5.21.1. The Committee noted that patients who received diflunisal had a less severe disease phenotype at baseline with younger age (P=0.07), lower BNP levels (P=0.008), lower troponin I levels (P=0.03) and a trend towards worse renal function, compared with patients who did not receive diflunisal.

5.21.2. The Committee noted that diflunisal was associated with improved survival that reportedly persisted after adjustment for several covariates (HR, 0.23, 95% CI: 0.09 to 0.60, P=0.003), however, the Committee considered the minimal amount of information available in abstract form and the imbalance between treated and untreated groups (suggesting appreciable selection bias) limited this evidence.

5.22. The Committee noted the following evidence regarding safety and tolerability of diflunisal in ATTR cardiomyopathy from retrospective longitudinal studies and an open-label study:

- Ikram et al. Amyloid. 2018;25:197-202 (N = 23)
- Sekijima et al. Amyloid. 2015;22:79-83 (N = 40)
- Castano et al. Congest Heart Fail. 2012;18:315-9 (N = 13)

5.22.1. The Committee noted these studies were limited by small numbers of patients and variation in the proportion of patients with each NYHA class (in particular, there were few patients with NYHA class IV). The Committee noted each study had a small number of patients withdraw, one study reported gastrointestinal toxicities and one study reported a trend towards decreased renal function over time.

5.23. The Committee also noted the following evidence regarding diflunisal in ATTR cardiomyopathy:

- Lohrmann et al. J Card Fail. 2019;S1071-9164:31435-6
- Wixner et al. Amyloid. 2019;26:39-40

5.24. The Committee noted that severe gastro-intestinal bleeding was not reported in any patients in the studies reviewed, although cases of erosive gastritis, reduced appetite and gastric pain were reported and did result in discontinuation for some patients. Members noted evidence from a Swedish study in 54 patients with ATTRm with neuropathy and considered that despite treatment discontinuation in 19% of patients (in part due to diarrhoea or increased creatinine), many patients tolerated treatment with diflunisal for many years (Wixner et al. Amyloid. 2019;26(sup1):39-40).

5.25. The Committee considered that the evidence supported the known NSAID side effect profile of diflunisal, with no unexpected or idiosyncratic toxicities identified. The Committee considered that management of patients with reduced or preserved EF (who may require different management) or with either heart failure or impaired renal function (in which case NSAIDs may be contraindicated) would be at their treating clinician's discretion, including the decision whether or not diflunisal was an appropriate treatment option.

5.26. The Committee considered that there was no evidence to indicate whether patients administered diflunisal are likely to have fewer cardiovascular-related hospitalisations than those who do not receive diflunisal.

5.27. The Committee considered that there is evidence of increased survival associated with diflunisal compared with best supportive care for patients with ATTRm cardiomyopathy or ATTRwt cardiomyopathy. The Committee considered that this assessment was based on low-quality evidence, with potential study bias caused by differences in the disease severity of the patient populations, small numbers of patients in the studies (and with

ATTRm, in particular), limited evidence for ATTRwt (noting there is an abstract only for one study in this patient group), and limitations of the evidence quality and strength.

5.28. The Committee considered that the evidence suggests the long-term survival benefit with diflunisal is possibly less than the long-term survival benefit with tafamidis, but noted that there were substantial limitations in this assessment as a result of the low quality and strength of the evidence, mentioned above.

5.29. Members considered that an additional benefit of diflunisal may be improvement of neuropathy from ATTR, although patients with neuropathy were not the target population in these applications and evidence for patients with ATTR cardiomyopathy with neuropathy was not reviewed in detail. Members considered that an improvement in neuropathy for patients with ATTR cardiomyopathy would likely be associated with improvement in quality of life for affected patients e.g. due to reduced postural hypotension.

5.30. The Committee also noted the following international consensus guidelines:

- Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology (Seferovic et al. Eur J Heart Fail. 2019;21:1169-1186).
- Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association (Kittleson et al. Circulation. 2020;142:e7-e22).
- The American College of Cardiology December 2019 update (based on the European Heart Journal article by Emdin et al. Eur Heart J. 2019;40:3699-706).
- Management of Cardiac ATTR. Australian Amyloidosis Network [Internet]. Australia; 2012 [cited 2020 July 21]. Available from http://amyloidosis.net.au/health-professionals/amyloidosis-for-cardiologists/

5.31. The Committee considered that the proposed Special Authority criteria for diflunisal identified a specific patient group with ATTR cardiomyopathy based on the evidence available (including NYHA class). The Committee did not consider at this stage that the Special Authority criteria for tafamidis required amendment in light of the evidence reviewed by the Committee for diflunisal.

5.32. The Committee considered that with an estimated 100 patients per year with ATTR cardiomyopathy that the cost to the pharmaceutical budget each year would be low, however, the Committee considered that the presence of a funded disease-modifying treatment for ATTR cardiomyopathy e.g. diflunisal, would likely increase the disease prevalence in New Zealand, due to greater awareness and diagnosis resulting in more patients being considered for treatment.

5.33. The Committee considered that funding a disease-modifying therapy for ATTR cardiomyopathy e.g. diflunisal, would also lead to increased use of health system resource for early diagnosis such as biopsies (either endomyocardial biopsy, or non-cardiac biopsy e.g. fat pad, cardiac MRI scans, or 99mtechnetium-pyrophosphate (99mTc-PYP) scans, if available.