Record of the Cardiovascular of PTAC meeting held at PHARMAC on 8 May 2019 (minutes for web publishing)

Cardiovascular Subcommittee minutes 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 Cardiovascular Subcommittee meeting; only the relevant portions of the minutes relating to Cardiovascular Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Cardiovascular Subcommittee 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.

These Subcommittee minutes will be reviewed by PTAC at its meeting on 8 & 9 February 2018, the record of which will be available in due course.

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Summary of recommendations

6.4 The Subcommittee **recommended** that alirocumab be funded for heterozygous familial hypercholesterolaemia (HeFH) with a high priority, based on the high heath need of this population and limited effective funded treatment options. The Subcommittee recommended that funding for this group (patients with HeFH) be subject to the following Special Authority criteria:

> **Special Authority for Subsidy**
> **Initial application – (heterozygous familial hypercholesterolaemia)** from a cardiologist, or relevant medical specialist on the recommendation of a cardiologist. Approvals valid for 2 years for applications meeting the following criteria:
> All of the following:
> 1. Treatment will be used in conjunction with dietary therapy and exercise; and
> 2. Patient has a diagnosis of heterozygous familial hypercholesterolaemia confirmed by either:
> 2.1. Genetic testing; or
> 2.2. A Dutch Lipid Clinic Network Score of 6 or greater; and
> 3. Either:
> 3.1. Patient has an LDL cholesterol level in excess of 3.3 mmol/litre and has symptomatic atherosclerotic cardiovascular disease; or
> 3.2. Patient has an LDL cholesterol level in excess of 5.0 mmol/litre; and
> 4. Any of the following:
> 4.1. Patient has been treated for at least 3 months at a maximum tolerated dose of an HMG CoA reductase inhibitor (statin) in conjunction with dietary therapy and exercise; or
> 4.2. Patient has developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating withdrawal of statin treatment; and
> 4.3. Treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.
>
> **Renewal – (heterozygous familial hypercholesterolaemia)** from any relevant practitioner on the recommendation of a cardiologist or relevant medical specialist. Approvals valid for 2 years where the treatment remains appropriate and the patient is benefiting from treatment.

6.5 The Subcommittee **recommended** that alirocumab be funded for acute coronary syndrome (ACS) with diabetes with a low priority based on the magnitude of health benefit from treatment for this group, and financial risk associated with treating a large patient population. The Subcommittee recommended that funding for this group (patients with ACS with diabetes) be subject to the following Special Authority criteria:

> **Special Authority for Subsidy**
> **Initial application – (acute coronary syndrome with diabetes)** from a cardiologist, or relevant medical specialist on the recommendation of a cardiologist. Approvals valid for 2 years for applications meeting the following criteria:
> All of the following:
> 1. Treatment will be used in conjunction with dietary therapy and exercise; and
> 2. Treatment will be used in conjunction with statin and/or other lipid lowering therapy; and
> 3. Either:
> 3.1. Patient has been hospitalised for an acute myocardial infarction; or

3.2. Patient has been hospitalised for unstable angina, and
4. Patient has diabetes mellitus; and
5. Patient has an LDL cholesterol level in excess of 2.59 mmol/litre; and
6. Either:
   6.1. Patient has had at least 3 months of treatment at a maximum tolerated dose of an HMG CoA reductase inhibitor (statin) plus ezetimibe, in conjunction with dietary therapy and exercise; or
   6.2. Patient has had at least 3 months of treatment with ezetimibe and has developed a clinically important product-related adverse event after a trial of treatment with at least two different HMG CoA reductase inhibitors (statins) necessitating withdrawal of statin treatment.

Renewal – (acute coronary syndrome with diabetes) from any relevant practitioner on the recommendation of a cardiologist or relevant medical specialist. Approvals valid for 2 years where the treatment remains appropriate and the patient is benefiting from treatment.

7.4 The Subcommittee **recommended** that tafamidis for the treatment of cardiac amyloidosis be funded with a medium priority based on high health need, the lack of funded pharmaceutical alternatives that modify disease progression and a high cost of treatment. The Subcommittee recommended funding with the following restrictions:

Special Authority for Subsidy
Initial application from a haematologist, cardiologist or relevant medical specialist on the recommendation of a haematologist. 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 has end-diastolic interventricular septal wall thickness of greater than 12 mm on echocardiography; and
4. Either:
   4.1. Patient has been hospitalised for heart failure; or
   4.2. Patient has clinical evidence of heart failure (without hospitalisation) requiring treatment with a diuretic; and
5. Patient's symptoms meet the criteria of the New York Heart Association (NYHA) Class I or II; and
6. Patient has an NT-proBNP of greater than 70 pmol/L; and
7. Patient has not received a liver or heart transplant, or implanted cardiac mechanical assist device.

Note: Patient must not use doxycycline, verapamil or diltiazem during treatment with tafamidis
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 or II; and
3. Patient has an NT-proBNP of greater than 70 pmol/L; and
4. Patient has not received a liver or heart transplant, or implanted cardiac mechanical assist device.

Note: Patient must not use doxycycline, verapamil or diltiazem during treatment with tafamidis.

7.5 The Subcommittee **recommended** that PHARMAC engage with Pfizer, the supplier of tafamidis, following the Subcommittee's positive recommendation.

8.3 The Subcommittee **recommended** that the application to widen access to eplerenone for patients with heart failure and diabetes, or heart failure with risk of diabetes, be declined. The Subcommittee recommended this because the SNOW trial showed that eplerenone would not in this group provide any additional benefits compared with spironolactone.

8.4 The Subcommittee **recommended** widening access to eplerenone for patients with primary aldosteronism who are also intolerant of spironolactone with a high priority. The Subcommittee considered there was a lack of alternative treatments for this patient group, and that studies demonstrated eplerenone would help with this condition.

8.5 The Subcommittee **recommended** widening access to eplerenone for patients with resistant hypertension who are also intolerant of spironolactone with a medium priority. The Subcommittee considered that this patient group had few effective treatments and there was generally evidence that eplerenone could treat hypertension.

9.3. The Subcommittee recommended widening access to sildenafil for PAH as follows, with a low priority (additions in bold, deletions in strikethrough):

Initial application — (Pulmonary arterial hypertension*) only from a respiratory specialist, cardiologist or medical practitioner on the recommendation of a respiratory specialist or cardiologist. Approvals valid without further renewal unless notified for applications meeting the following criteria:

All of the following:
1 Patient has pulmonary arterial hypertension (PAH)*; and
2 Any of the following:
- 2.1 PAH is in Group 1 of the WHO (Venice) clinical classifications; or
- 2.2 PAH is in Group 4 of the WHO (Venice) clinical classifications; or
- 2.3 PAH is in Group 5 of the WHO (Venice) clinical classifications; and

~~3 Any of the following:~~
- ~~3.1 PAH is in NYHA/WHO functional class II; or~~
- ~~3.2 PAH is in NYHA/WHO functional class III; or~~
- ~~3.3 PAH is in NYHA/WHO functional class IV; and~~

~~4~~ Either:
- 4.1 All of the following:
  - 4.1.1 Patient has a pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mmHg; and
  - 4.1.2 Either:
    - 4.1.2.1 Patient has a mean pulmonary artery pressure (PAPm) > 25 mmHg; or
    - 4.1.2.2 Patient is peri Fontan repair; and
  - 4.1.3 Patient has a pulmonary vascular resistance (PVR) of at least 3 Wood Units or at least 240 International Units (dyn s cm-5); or
- 4.2 Testing for PCWP, PAPm, or PVR cannot be performed due to the patient's young age.

Note: Indications marked with * are unapproved indications

The Subcommittee considered that the criteria proposed for deletion above either are not limiting access, so are unnecessary, or are not required given sildenafil's low cost.

9.4. The Subcommittee recommended widening access to medicines for PAH to allow first-line dual therapy (that is, to remove the requirement to trial a monotherapy) with a high priority. Members considered that there was evidence to support first-line dual therapy in general.

9.5. The Subcommittee recommended that PTAC approach suppliers of tadalafil, as there is better evidence for tadalafil and for sildenafil in some treatment pathways.

1. Record of Subcommittee meeting held 27 September 2017

1.1. The Subcommittee reviewed the minutes of the 27 September 2017 Cardiovascular Subcommittee and agreed that the minutes be accepted.

Aspirin, atorvastatin, and ramipril combination pill (Trinomia, a polypill)

1.2. The Subcommittee noted that PTAC had recommended against funding aspirin, atorvastatin, and ramipril combination pills.

1.3. The Subcommittee noted that at its September 2017 meeting it had considered the evidence for the Trinomia polypill and that it had considered that there was evidence (Bahiru et al, Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD009868) to support a benefit to adherence from a polypill, and to support a benefit in surrogate markers (e.g. reduction in BP and lipid levels) for cardiovascular disease in a similar magnitude to that of the individual agents (aspirin, statins and ACE inhibitors).

1.4. Some Members considered that surrogate markers have been accepted as sufficient evidence to fund other cardiovascular medicines, eg ezetimibe. In addition, some Members considered that the clinical outcomes of the individual agents of the polypill (aspirin, atorvastatin and ramipril) are well known and for this reason, trials demonstrating clinical outcomes for the polypill were not necessary. Some Members considered that from a practical perspective it is likely that there would be improved adherence from a polypill; which would be likely to translate into improved health outcomes for patients. However, some Members considered that evidence in the form of good quality, well-designed trials with hard cardiovascular outcomes was needed.

1.5. The Subcommittee considered that there were a number of funded combination products in the diabetes, HIV, and respiratory therapeutic groups for which additional trials demonstrating clinical outcomes over and above the individual agents had not been necessary.

1.6. The Subcommittee considered that there remains an issue that fixed-dose combination products may not contain the right ratio of doses for any given person, and that this issue should be accounted for when considering such products. Some members considered that that polypills may provide the greatest health benefit in secondary prevention, rather than primary prevention as aspirin is now rarely used in primary prevention. However, Members considered that there was no available published evidence to support this statement.

1.7. Members considered that funding a polypill may provide an opportunity to improve equity of access, as adherence is, anecdotally, worse in certain groups, and noted that patients would have less co-pays to pay to receive a combination product instead of three individual agents. However, some Members considered that there are a myriad of other factors that may affect adherence, such as education.

1.8. Some Members of the Subcommittee did not agree with PTAC's recommendation, and some Members **recommended** that PTAC review this application again with consideration to the points the Subcommittee has raised.

Ranolazine

1.9. The Subcommittee noted that it had previously recommend funding "an additional treatment for refractory angina" which could be "either ranolazine or nicorandil (although preferably both)". The Committee also noted that nicorandil has since been funded, and noted that the supplier of ranolazine is now not willing to make an offer to supply.

1.10. Members considered that ranolazine could still be an important drug for a niche market.

Rosuvastatin

1.11. The Subcommittee noted that both it and PTAC had recommended funding rosuvastatin previously.

1.12. The Subcommittee noted that the chemical was off-patent. Members considered that there is some evidence that rosuvastatin is more effective than other statins and ezetimibe, due to its potency, and considered that pravastatin was of lower benefit given the high levels of cardiovascular disease in New Zealanders. Members considered that clinicians are prescribing higher doses of atorvastatin, and that there is a need for an alternative for patients unable to tolerate atorvastatin, or with persisting LDL elevation despite full-dose atorvastatin. Members considered that currently funded treatments are not effective for all patients to achieve target lipid levels. Members considered that in practice they are only able to achieve lipid target levels for around 30% of patients.

1.13. The Subcommittee noted that PHARMAC is now considering PCSK9 inhibitors, which are significantly more expensive than statins. The Subcommittee considered that rosuvastatin would provide additional benefits over currently funded treatments, at a much lower cost than PCSK9 inhibitors. Some Members considered that funding rosuvastatin may allow more rational assessment of who should receive PCSK9 inhibitors, should they be funded.

1.14. Members raised issues with the toxicity of rosuvastatin, especially in women and in the elderly, and that this has been seen through use in Australia. Members also considered that patients in Australia are ending up on much higher doses than studies would support, and therefore rosuvastatin, in a real-world setting, may not be as effective as marketing by pharmaceutical suppliers would suggest.

1.15. The Subcommittee considered that rosuvastatin remains an important medicine, and that it is the most commonly supplied statin in the world. The Subcommittee considered that moving the statin market to such a widely used statin would reduce supply risk, whereas there could be supply risks if much of the New Zealand market continues using simvastatin and atorvastatin.

1.16. The Subcommittee noted that PTAC had given a medium priority, as opposed to the high priority that the Subcommittee gave in 2017. No consensus was formed on accepting PTAC's recommendation.

2. Therapeutic Group and NPPA Review

Alpha-adrenoreceptor blockers

2.1. The Subcommittee discussed supply risks around alpha-adrenoreceptor blockers. The Subcommittee considered that these agents were mostly used for treating benign prostatic hyperplasia and that it was vital to retain a supplier of doxazosin and terazosin, with a preference to retain doxazosin. The Subcommittee discussed tamsulosin as a possible alternative. The Subcommittee noted that prazosin was also used off-label as a treatment for post-traumatic stress disorder. The Subcommittee **recommended** PHARMAC seek clarification on these points from urologists and psychiatrists around their use and importance.

2.2. The Subcommittee noted that there was low use of phenoxybenzamine hydrochloride and phentolamine but considered there were few if any uses of these agents for cardiovascular indications. Members considered that phenoxybenzamine and phentolamine were used for treatment of pheochromocytoma, and that there were other limited funded alternatives. The Subcommittee suggested that PHARMAC seek further advice from endocrinologists about the clinical indications of these treatments.

Agents Affecting the Renin-Angiotensin System

2.3. The Subcommittee noted that use of combination products containing ACE inhibitors with diuretics has been decreasing, and considered some possible reasons. Members noted that BPAC had published advice around the risks of prescribing the “Triple Whammy” (ACE inhibitor, diuretic and NSAID), and the importance of reducing prescribing of this combination. Members also noted a slight increase in angiotensin receptor blockers (ARBs), and considered that prescribing practice is shifting to using ARBs first-line. Members also speculated that people moving from Australia may be staying on the treatment (ARBs) that they began there.

2.4. [Information withheld]

2.5. The Subcommittee noted that use of perindopril was rising, which members considered was due to educational materials persuading clinicians to move away from cilazapril.

2.6. The Subcommittee noted the supply issues around cilazapril products. The Subcommittee considered that if combination cilazapril plus hydrochlorothiazide was unavailable, then patients would use either a different ACE inhibitor with a different diuretic, or instead would use another funded combination product such as quinapril with hydrochlorothiazide or losartan with hydrochlorothiazide. The Subcommittee considered that transitioning patients with heart failure would be the most challenging; but that the majority of patients with heart failure would not be on the combination product.

2.7. The Subcommittee considered that cilazapril has little clinical outcome data. The Subcommittee considered that if cilazapril was unavailable, then other ACE inhibitors would be appropriate alternatives. Members considered that some patients could also switch to an ARB, and that candesartan would be an appropriate option. Members considered that ramipril and quinapril are the most common agents globally, and there remains a need to secure supply of ramipril for New Zealand. Members considered that heart failure patients would be the most difficult to transition.

2.8. The Subcommittee discussed ways to raise awareness of supply issues and support changes in ACE inhibitor prescribing practice. Members highlighted NZ Doctor, the NZ Formulary, local Health Pathways, BPAC, Goodfellow, DHB guidance, college conferences, and continuing medical education as places where GPs and clinicians get information. Members considered there would be a need for clear conversion tables to find the right dose, and regimen, if switching medicines. Members considered that a focus on junior doctors in hospitals was important as they are often the ones to initiate these medicines. In addition, Members considered that year 1 General Practice Education Programme (GPEP-1) registrars would be a good group to target, as would have significant influence on future prescribing practices. Members also considered it was valuable to have one clear message for clinicians rather than multiple.

2.9. Members considered that initiation of an ACE inhibitor was often done in secondary care, so targeting prescribing practice in secondary care would be an important first step to discourage use of cilazapril.

2.10. The Subcommittee noted that use of losartan has been rising and that it would soon overtake candesartan for units dispensed. Members considered this was due to increased familiarity with the agents.

Antiarrhythmics

2.11. The Subcommittee noted the decrease in use of antiarrhythmics, particularly amiodarone, and considered this was likely due to increased use of devices to treat cardiac arrhythmias and better treatment generally. Members considered it could also be due to more confidence in other agents, such as flecainide, and concerns around amiodarone's toxicity.

2.12. The Subcommittee discussed agents in this class which have little use. Members considered that antiarrhythmics in general did not have good efficacy but there were few alternatives for difficult to treat arrythmias.

2.13. Members considered that mexiletine was used by specialists for difficult to treat arrythmias, such as long QT syndrome and some ventricular tachycardias.

2.14. Members considered that disopyramide and propafenone have niche roles such as treatment of hypertrophic cardiomyopathy. However, the Subcommittee also noted that none of its members had personal expertise with this area.

2.15. The Subcommittee noted that likely alternatives to mexiletine, disopyramide and propafenone could include prolonged hospital admissions and VT ablation for some patients.

2.16. The Subcommittee noted the recent decision to change the funded brands of flecainide. It considered that the consultation on this was good and that the outcome would mean substantial savings. The Subcommittee considered that plasma monitoring could be considered for children. The Subcommittee also considered that patients on flecainide are mainly supported by a GPs and considered that years could go for years without a patient seeing a cardiologist, and that even then they would often be seen by a cardiology nurse instead. Members considered there were marked differences in treatment practice and knowledge around the country. Members considered that ensuring GPs are well informed about the brand change was important.

2.17. The Subcommittee discussed ivabradine, which it had previously recommended funding for inappropriate sinus tachycardia (IST) with a high priority. The Subcommittee also noted that PTAC had recommended that it review ivabradine once its registration had been approved. The Subcommittee also noted that no ivabradine product was registered and that there no applications to Medsafe for registration have been made.

2.18. The Subcommittee considered that since there is a small market for ivabradine, there was little incentive for a supplier to pay the costs of registration. Members considered that because the market was small, the risk from using an unregistered medicine was also small. Members also considered that there remains a high unmet health need for patients with IST intolerant to funded agents, and that ivabradine would provide a health benefit for this niche group of patients. Members considered the group with IST that would access ivabradine if it was funded was likely to be small; potentially being as low as 10 new patients per year.

2.19. The Subcommittee **recommended** that PHARMAC continue to investigate options to fund ivabradine even if the product was unregistered.

Antihypotensives

2.20. The Subcommittee noted the increasing use of midodrine. Members considered that this may be due to greater awareness, possibly due to geriatricians prescribing this more, and other clinicians seeing these patients and learning from this. The Subcommittee considered that the increase in use was unlikely to be due to clinicians not following the Special Authority; the Special Authority is generally loose and leaves much to the opinion and discretion of the prescriber.

Beta-adrenoreceptor blockers

2.21. The Subcommittee noted that use of bisoprolol fumarate is increasing, and considered this was appropriate as it was consistent with the evidence of benefit from the latest clinical trials.

2.22. The Subcommittee noted that labetalol injections were only partly funded in community. Members were surprised that there was any community use, given the support needed to administer it, and speculated it may be used in rural practices. Given this, the Subcommittee considered there would be low risk of additional spend if the product was fully funded, as it is already in hospitals.

2.23. The Subcommittee **recommended** that labetalol injections be fully funded in the community.

Calcium channel blockers

2.24. The Subcommittee noted the rise in prescriptions in this group, and considered that these agents work well in hypertension, while beta blockers do not, so considered that there could be a move from that group to this one. Members also considered that thiazides have safety risks regarding renal toxicity and that there is a move from thiazides to calcium channel blockers for this reason. The Subcommittee expected that the rises seen recently in calcium channel blockers will continue, but that rises would not be considerable.

2.25. [Information withheld] The Subcommittee considered that verapamil is used for a number of niche indications including treatment of hypertrophic cardiopathy where patients are contraindicated to use of a beta-blocker (e.g. those with asthma); a subset of patients with VT and those patients who have experienced unacceptable

oedema from other calcium channel blockers; those patients unable to take coronary disease unable to tolerate beta-blockers or diltiazem; rate control for some patients with AF; and, treatment of cluster headache and migraine. The Subcommittee noted that there are several hundreds of patients who take verapamil, but that it is unlikely to be used in any patients for whom there would be another funded alternative, due to the frequency of dosing and adverse effects of constipation.

2.26. The Subcommittee considered that there is unlikely to be suitable funded alternatives for the majority of patients taking verapamil. The Subcommittee also suggested asking neurologists for further advice on non-cardiovascular uses.

Centrally-acting agents

2.27. The Subcommittee considered that clonidine is primarily used in pain management and opioid withdrawal rather than cardiovascular uses, and did not expect increase in clonidine use for cardiovascular indications.

Diuretics

2.28. The Subcommittee noted that there had recently been an increase in the price of bendroflumethiazide, such that while use has been steadily falling, total spend on the chemical is higher. Members discussed whether use of bendroflumethiazide would continue to fall. Members considered that there is increased education around the differences in thiazides, and around whether doses can be lowered to reduce toxicity without reducing effectiveness.

2.29. Members noted that metolazone had had its restrictions removed recently. Members considered this was unlikely to lead to much increased use as the medicine is only used for fixed periods of time.

Lipid-modifying agents

2.30. The Subcommittee noted that the price of ezetimibe had decreased but ezetimibe was still subject to a Special Authority. The Subcommittee considered that Special Authority applications do take time to complete, and that removing this administrative burden would be of benefit. The Subcommittee also considered that patients sometimes are unable to get prescriptions on a given day due to a Special Authority expiring, leading to breaks and delays in treatment.

2.31. Members discussed how much use of ezetimibe would increase if its Special Authority was removed. The Subcommittee considered that ezetimibe is an ineffective treatment. Members considered that because ezetimibe is not a popular agent, this would limit any increase. However, members considered that people are always looking for an alternative and widening access would encourage use. Members considered that in Australia, supplier marketing encourages first-line dual therapy and if the Special Authority was removed, then this indication could also become encouraged in NZ. Members considered that removing the Special Authority could be seen as endorsing its use, which would be a negative consequence of the action.

2.32. The Subcommittee did not reach a conclusion on whether the ezetimibe Special Authority should be removed but considered it would provide benefits in reduced breaks in treatment and a reduction in administrative burden, compared with the costs of some number of additional patients taking a poorly effective medicine.

2.33. Members noted that we currently spend approximately $1 million each year on bezafibrate each year and considered that such a high spend for this chemical seemed inappropriate given that bezafibrate was a relatively ineffective treatment.

Nitrates

2.34. The Subcommittee noted that the use of nitrates has been decreasing, and considered this was likely due to better management of ischaemic heart disease.

Sympathomimetics

2.35. The Subcommittee noted that isoprenaline had a part charge in community. The Subcommittee considered that community use was extremely low, as this was a hospital-only medicine, and so considered there would be little risk of increased use if it was fully funded in the community.

2.36. The Subcommittee **recommended** that isoprenaline be fully funded in the community.

Vasodilators

2.37. The Subcommittee noted that use of vasodilators has been increasing, and considered this may reflect new guidelines on the treatment of PAH, and so generally reflects catching up on practice in the rest of the world.

Antithrombotic agents (Blood and blood forming organs)

2.38. The Subcommittee reviewed the use of rivaroxaban since it was open listed from 1 June 2018. The Subcommittee considered that rivaroxaban would largely replace use of enoxaparin in the management of DVT/PE as enoxaparin is inconvenient to administer, taking five days, whereas rivaroxaban is a standard tablet. Members also noted that rivaroxaban is taken once-daily and considered that this was attractive. Members noted that there was no reversal agent for rivaroxaban, but considered this would not limit prescribing. Members also noted that some prescribers would continue to use enoxaparin as it is easier to reverse compared with rivaroxaban and only a few hours are required to wait prior to procedures when enoxaparin is used.

2.39. The Subcommittee discussed the need for further direct anticoagulants given the open access to dabigatran and rivaroxaban. Members considered that rivaroxaban is well tolerated, and though it can cause some renal impairment the risk is lower than for dabigatran. Members noted that apixaban is taken twice daily. Some members considered there was no current unmet health need and therefore no clinical need for apixaban. Others considered that apixaban is the agent with the best evidence and would have been first priority if PHARMAC were to fund just one agent. Members also discussed that a lack of a reversal agent for an anticoagulant can delay surgery and cause harm.

2.40. The Subcommittee considered that use of rivaroxaban will continue to increase, predominantly due to ease of administration and dosing, and Members estimated that in the future there could be a 10:1 ratio of use of rivaroxaban to dabigatran.

2.41. The Subcommittee noted that a supplier had expressed interest in supplying reteplase, and that there had recently been large price increases for alteplase and tenecteplase. Members considered that clinicians are currently familiar with using

tenecteplase, that it is easy to administer via two bolus injections, and that having multiple agents could cause issues. The Subcommittee considered that thrombolytics were also used in the treatment of stroke and pulmonary embolism and suggested that PHARMAC could seek the view of the Neurology and Respiratory Subcommittees if further clinical advice was required.

Diabetes agents with cardiovascular benefits

2.42. The Subcommittee reviewed the Diabetes Subcommittee minutes from March 2019 relating to DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists.

2.43. Members considered that weight gain from the currently funded antidiabetic agents remains an issue. The Subcommittee noted that the criteria recommended by the Diabetes Subcommittee referred to "a validated cardiovascular risk calculator" but did not specify which one.

2.44. Members considered that internationally, these medicines were being viewed less as diabetes medicines and more as cardiovascular medicines, and that their place in treatment was moving more to primary and secondary prevention of cardiovascular disease. Members considered that there are two groups who could benefit from these agents: those with diabetes and established cardiovascular disease; and those with diabetes and a high cardiovascular risk. Members considered that overall mortality is the most important outcome to patients, so care was needed interpreting clinical meaningfulness of health benefits, for medicines showing only cardiovascular outcomes.

2.45. Members considered that diabetes clinical guideline have not been updated since the disestablishment of the NZ Guidelines group. Members noted that BPAC last updated its guidance on diabetes 3.5 years ago and considered that if any new medicines were funded then that would be an ideal time for PHARMAC to request BPAC to update that guidance.

2.46. Members endorsed the Diabetes Subcommittee recommendations that both SGLT-2 inhibitors and GLP-1 receptor agonists become funded in NZ, with high priority.

Equity access to cardiovascular medicines

2.47. The Subcommittee reviewed a paper from PHARMAC staff outlining the scale to which Māori patients have inequitable access to already funded cardiovascular medicines, including adjustments for burden of disease.

2.48. The Subcommittee considered that the data presented by PHARMAC staff highlighted an issue for Māori people with regards to persistence (ongoing treatment, as opposed to initiations on treatment). The Subcommittee considered that a large cause of inequity was access to primary care, and that access to primary care was driven by cost. The Subcommittee considered that patient groups with adequate financial resource are more likely to comply with follow up appointments post initiation of treatments than those who are financially constrained. The Subcommittee considered that the juncture of secondary care initiation and primary care continuation of therapy was likely to affect access to medicines for those who could not afford the time or cost of attending primary care appointments required for ongoing monitoring of treatment between the two settings.

2.49. The Subcommittee noted a lack of Māori and Pacific participants in clinical trials of new medicines, leading to a lack of an ethnic specific evidence base for efficacy and effectiveness of medicines.

2.50. The Subcommittee considered that polypills, of which one example was Trinomia discussed above, would make adherence easier and would reduce personal cost by reducing co-payments to patients. Members also talked about favouring once-daily medicines for ease of adherence, though some considered that in practice this would not have much impact. Members also considered that medication adherence is an issue that affects the general population and should not be seen as a Māori issue only.

2.51. Members discussed how barriers could be removed to accessing regular prescriptions. Members noted that new apps are assisting patients in requesting prescriptions more easily, and that smartphone usage was widespread except in the most deprived group (NZDep quintile 5), though noted access to internet data can be a problem. Members considered that in practice pharmacists don't usually arrange with a patient's clinician for repeats, but that a more proactive pharmacy model could improve medicine access equity. Members considered that general practice management systems are getting better about identifying people who are not taking their medication.

2.52. The Subcommittee considered that much of the changes needed to address overall medicine access inequity would need to be at government level, such as tax credits, removal of pharmacy co-payments, and funding of GP visits. Members suggested that PHARMAC could use the data presented at this meeting to influence the Government to make changes through Government policies.

2.53. The Subcommittee also considered that adopting cultural perspectives is likely to play a role in improving persistence with medicines for long term conditions. The Subcommittee considered that changes for improving medicine access equity coming from within an affected group would be more sustainable than imposing changes from the outside.

2.54. Members acknowledged that while eliminating inequities in access to medicines was a complex issue and required multiple solutions which largely were not within PHARMAC's control, there was some opportunity as a Subcommittee to provide advice that could incrementally improve medicine access equity.

3. Correspondence and Matters Arising

3.1. The Subcommittee reviewed correspondence from an applicant who had sought to incorporate genetic testing into the funding criteria for ticagrelor and prasugrel. The application proposed that funding of these agents be restricted to patients who have undergone a genetic test, and that funding may be widened or narrowed depending on the result of that test.

3.2. The Subcommittee noted that, at its September 2017 meeting, it had previously deferred making a recommendation until more evidence was available. Since then, the applicant had provided further correspondence, including an additional study (Notarangelo et al. J Am Coll Cardiol. 2018;71:1869-1877 – the PHARMCLO trial).

3.3. The Subcommittee noted that the PHARMCLO trial was a phase 3 randomised control trial that aimed to evaluate whether clinician knowledge of a patient's genetic characteristics resulted in better health outcomes for patients requiring antiplatelet

therapy. Patients were randomised to either undergo genetic testing for CYP2C19*2 and CYPC19*17 polymorphisms, or to undergo no genetic testing. Each patient's treating clinician then used all standard information, plus genetic testing if available, to select an antiplatelet agent. The primary endpoint was a composite endpoint, being met if a patient had any one of cardiovascular death, nonfatal myocardial infarction, stroke, or major bleeding, within 12 months of randomisation.

3.4. The Subcommittee noted that the PHARMCLO study reported a significant reduction in the primary endpoint in the genetic testing arm (HR 0.58; 95 CI 0.43-0.78; $p < 0.001$).

3.5. Members considered that this difference was large, and that it was biologically implausible for genetic testing to provide such a large benefit. The Subcommittee noted that patients in the genetic testing arm were considerably more likely to be prescribed ticagrelor (43% vs 33%), and considered that ticagrelor was generally a more effective medicine than both clopidogrel and prasugrel, so this could explain at least some of the difference in outcomes seen between arms.

3.6. Members considered that this trial design did not provide a definitive answer on whether targeted funding of these agents should be guided by genetic testing. Members considered that was also markedly underpowered, as it only enrolled one quarter of the planned study population.

3.7. Members also considered that there was no current consensus on how to manage patients with known genetic polymorphisms, specifically whether further/increased dose adjustments would be required for patients with alternative pharmacokinetic profiles arising from genetic polymorphisms. The Subcommittee consequently considered that it might be preferable to titrate the dose of each antiplatelet based on known drug levels in the blood, rather than change to alternate antiplatelet therapy.

3.8. Members considered that the cost of genetic testing is coming down. Members considered that there is a potential for such a system to benefit Māori and Pacific peoples as these populations have twice the prevalence of these genetic polymorphisms; however there was no real world data to support this at present.

3.9. Members considered a review of this issue by Klein et al 2019 (Arterioscler Thromb Vasc Biol. 2019;39:647–652), in which the authors highlight that results of large, ongoing, randomised controlled trials comparing a genotyping strategy to conventional treatment offers the potential to change how antiplatelet therapy is selected in cardiovascular patients . Members noted that there are two ongoing trials on this subject: TAILOR-PCI (Clinical Trials.gov identifier NCT01742117) and the POPular Genetics trial (Clinical Trials.gov identifier NCT01761786).

3.10. The Subcommittee considered that there was currently insufficient evidence to make a recommendation on this proposal. Instead, the Subcommittee **deferred making a recommendation** until the publication of TAILOR-PCI (Clinical Trials.gov identifier NCT01742117) and the POPular Genetics trial (Clinical Trials.gov identifier NCT01761786).

4. Alirocumab for the prevention of cardiovascular events in adults with hypercholesterolaemia

Application

4.1. The Subcommittee reviewed the application submitted by Sanofi for alirocumab for the prevention of cardiovascular events in adults with hypercholesterolaemia; specifically indicated for patients with heterozygous familial hypercholesterolaemia (HeFH), and for patients with acute coronary syndrome (ACS) with diabetes.

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

Recommendation

4.3. The Subcommittee **recommended** that alirocumab be funded for heterozygous familial hypercholesterolaemia (HeFH) with a high priority, based on the high heath need of this population and limited effective funded treatment options. The Subcommittee recommended that funding for this group (patients with HeFH) be subject to the following Special Authority criteria:

> **Special Authority for Subsidy**
> **Initial application – (heterozygous familial hypercholesterolaemia)** from a cardiologist, or relevant medical specialist on the recommendation of a cardiologist. Approvals valid for 2 years for applications meeting the following criteria:
> All of the following:
> 5. Treatment will be used in conjunction with dietary therapy and exercise; and
> 6. Patient has a diagnosis of heterozygous familial hypercholesterolaemia confirmed by either:
> 6.1. Genetic testing; or
> 6.2. A Dutch Lipid Clinic Network Score of 6 or greater; and
> 7. Either:
> 7.1. Patient has an LDL cholesterol level in excess of 3.3 mmol/litre and has symptomatic atherosclerotic cardiovascular disease; or
> 7.2. Patient has an LDL cholesterol level in excess of 5.0 mmol/litre; and
> 8. Any of the following:
> 8.1. Patient has been treated for at least 3 months at a maximum tolerated dose of an HMG CoA reductase inhibitor (statin) in conjunction with dietary therapy and exercise; or
> 8.2. Patient has developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating withdrawal of statin treatment; and
> 8.3. Treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.
>
> **Renewal – (heterozygous familial hypercholesterolaemia)** from any relevant practitioner on the recommendation of a cardiologist or relevant medical specialist. Approvals valid for 2 years where the treatment remains appropriate and the patient is benefiting from treatment.

4.4. The Subcommittee **recommended** that alirocumab be funded for acute coronary syndrome (ACS) with diabetes with a low priority based on the magnitude of health benefit from treatment for this group, and financial risk associated with treating a large patient population. The Subcommittee recommended that funding for this group (patients with ACS with diabetes) be subject to the following Special Authority criteria:

> **Special Authority for Subsidy**

Initial application – (acute coronary syndrome with diabetes) from a cardiologist, or relevant medical specialist on the recommendation of a cardiologist. Approvals valid for 2 years for applications meeting the following criteria:
All of the following:

8. Treatment will be used in conjunction with dietary therapy and exercise; and
9. Treatment will be used in conjunction with statin and/or other lipid lowering therapy; and
10. Either:
    3.1. Patient has been hospitalised for an acute myocardial infarction; or
    3.2. Patient has been hospitalised for unstable angina, and
11. Patient has diabetes mellitus; and
12. Patient has an LDL cholesterol level in excess of 2.59 mmol/litre; and
13. Either:
    12.1. Patient has had at least 3 months of treatment at a maximum tolerated dose of an HMG CoA reductase inhibitor (statin) plus ezetimibe, in conjunction with dietary therapy and exercise; or
    12.2. Patient has had at least 3 months of treatment with ezetimibe and has developed a clinically important product-related adverse event after a trial of treatment with at least two different HMG CoA reductase inhibitors (statins) necessitating withdrawal of statin treatment.

Renewal – (acute coronary syndrome with diabetes) from any relevant practitioner on the recommendation of a cardiologist or relevant medical specialist. Approvals valid for 2 years where the treatment remains appropriate and the patient is benefiting from treatment.

Discussion

Heterozygous familial hypercholesterolaemia (HeFH)

4.5. The Subcommittee noted that heterozygous familial hypercholesterolemia (HeFH) is the most common of two subtypes of familial hypercholesterolaemia and is an inherited genetic disorder which causes high levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) from an early age, resulting in premature atherosclerosis. The Subcommittee noted that patients with HeFH have a high risk of cardiovascular disease which can occur from about 30 years of age (compared to over 60 years of age in those without HeFH), and a high risk of myocardial infarction (MI) and stroke.

4.6. The Subcommittee noted that the prevalence of HeFH is at least 1 in 500 and could be closer to 1 in 250, and that the applicant estimated that up to 460 New Zealand patients with HeFH could be eligible for the proposed treatment. The Subcommittee considered that patients with HeFH are a small group with a predictable disease course, especially in patients with a family history of HeFH, a previous cardiac event and high LDL-C.

4.7. The Subcommittee considered that patients with HeFH have a high heath need and have significant morbidity and mortality. The Subcommittee considered that while agents such as atorvastatin are currently used to treat patients with HeFH, there are limited effective treatments available for the patients who require lifelong treatment. The Subcommittee considered that patients with HeFH would benefit from LDL-C lowering over time and that lowering of high LDL-C levels is important in this patient group.

Acute coronary syndrome (ACS) with diabetes

4.8. The Subcommittee noted that acute coronary syndrome (ACS) refers to a previous acute cardiac event, either MI or unstable angina. The Subcommittee noted that patients with ACS can present with comorbidities such as diabetes and hypertension, that patients with diabetes who experience an ACS have poorer health outcomes than those without diabetes, and that patients with diabetes are at substantially higher risk of cardiovascular disease (CVD) than patients without diabetes.

4.9. The Subcommittee noted that the applicant estimates that the prevalence of patients with a history of ACS in New Zealand is 3.8% and that this will remain constant, resulting in approximately 3,000 patients with ACS with diabetes who could be eligible for the proposed treatment. The Subcommittee noted that approximately one third of patients with ACS have concomitant diabetes. The Subcommittee considered that the group of patients with ACS with diabetes is a large, growing, high-risk population.

4.10. The Subcommittee considered that patients with ACS with diabetes are at high risk of subsequent cardiovascular events despite lifelong treatment with current therapies, due to the influence of other risk factors. The Subcommittee considered that, within this population of patients with ACS with diabetes, the subgroup of patients who are intolerant of statins or on high-dose statin therapy with high LDL-C would be those with the highest health need.

Discussion

4.11. The Subcommittee noted that the application was for funding of the monoclonal antibody alirocumab, an inhibitor of proprotein convertase subtilisin kexin type 9 (PCSK9).

4.12. The Subcommittee noted that alirocumab binds to PCSK9, increasing the number of LDL receptors which can remove more LDL-C from the circulation. Members considered that use of antibodies for LDL-C reduction is a relatively new treatment strategy in CVD.

4.13. The Subcommittee considered the specific evidence for alirocumab in patients with HeFH comes from the phase III, randomised, placebo-controlled ODYSSEY FH I trial (Kastelein et al. Eur Heart J. 2015:36;2996-3003) which investigated alirocumab compared to placebo in 486 patients with HeFH; and, the phase III, randomised, placebo-controlled ODYSSEY FH II trial (Kastelein et al. Eur Heart J. 2015:36;2996-3003) which investigated alirocumab and lipid modifying therapy compared to placebo in 249 patients with HeFH.

4.14. The Subcommittee considered that the results of the ODYSSEY FH I and FH II trials demonstrated a significant reduction in LDL-C with alirocumab in patients with HeFH. The Subcommittee noted that patients in both trials had inadequately controlled LDL-C levels at baseline despite maximally tolerated statin, with or without other lipid-lowering therapy, and members considered that the definition of 'inadequately controlled' could vary.

4.15. The Subcommittee noted that the applicant conducted two indirect treatment comparisons (ITCs) of alirocumab compared to evolocumab (an unfunded agent in the same class which is indicated for the treatment of both subtypes of familial hypercholesterolaemia). The Subcommittee noted that the ITCs used clinical trials of alirocumab (ODYSSEY FH I and ODYSSEY FH II, referenced previously) and of evolocumab (RUTHERFORD [Raal et al. Circulation. 2012:126;2408-17] and

RUTHERFORD-2 [Raal et al. Lancet. 2015: 385;331-40]) to assess LDL-C change between baseline and week 12, and between week 12 and week 24 in patients with HeFH. The Subcommittee noted that the supplier stated that the results of the ITCs indicated that alirocumab has non-inferior efficacy to evolocumab.

4.16. The Subcommittee noted the primary evidence supplied in support of this application is from the randomised, phase III, double-blind, placebo-controlled ODYSSEY OUTCOMES trial which investigated alirocumab (75 mg two-weekly) compared to matching placebo in 18,924 patients over the age of 40 years who have ACS, have LDL-C of at least 1.8 mmol/L and are receiving high-dose statin treatment (Schwartz et al. N Engl J Med. 2018. 379; 2097-2107). The Subcommittee noted this publication presents results after median follow-up of 2.8 years.

4.17. The Subcommittee noted that the Schwartz et al. publication did not detail how many of the ODYSSEY OUTCOMES trial participants had HeFH, nor were there results of subgroup analysis of outcomes for patients with HeFH. The Subcommittee considered that the primary evidence could be applied to the broader population of patients with hypercholesterolaemia, and that the low LDL-C level for entry criteria also indicated a wide patient population. Members considered it was unclear whether the ODYSSEY OUTCOMES trial data could be applied to patients not receiving treatment with a statin and noted that a small number of statin-intolerant patients were enrolled in the trial.

4.18. The Subcommittee noted the primary endpoint of ODYSSEY OUTCOMES was the composite of death from coronary heart disease (CHD), nonfatal MI, fatal or non-fatal ischemic stroke, unstable angina requiring hospitalisation; this was reported to be 9.5% in the alirocumab group compared to 11.1% in the placebo group (HR 0.85, 95% CI 0.78 to 0.93, P<0.001). The Subcommittee considered that the ODYSSEY OUTCOMES trial demonstrated the greatest benefit from alirocumab occurred in patients with higher baseline LDL-C.

4.19. The Subcommittee noted the composite endpoint of death from any cause in ODYSSEY OUTCOMES was reported to be 10.3% in the alirocumab group compared to 11.9% in the placebo group (HR 0.86, 95% CI 0.79 to 0.93, P<0.001).The Subcommittee considered this result indicated a significant benefit of alirocumab compared to placebo in the wider population of patients with hypercholesterolaemia. The Subcommittee considered that this benefit (reduction in risk of death from any cause) was not seen in data provided for the funding application for evolocumab (for treatment of both subtypes of familial hypercholesterolaemia) which was recommended for decline in 2018.

4.20. The Subcommittee noted that the ODYSSEY OUTCOMES trial included patients who received treatment with different statins at a variety of doses, including the unfunded agent rosuvastatin which is currently under assessment by PHARMAC, meaning that some aspects of this trial may not be generalisable to the New Zealand population. Members noted that the trial included patients from New Zealand.

4.21. The Subcommittee noted the results of several clinical trials investigating alirocumab for patients at high risk of CV events compared alirocumab to placebo or compared to ezetimibe. The Subcommittee considered the results of these clinical trials all reported significant reduction in LDL-C and other lipid markers with alirocumab:

- Roth et al. Future Cardiol. 2015:11;27-37: ODYSSEY MONO

- Moriarty et al. J Clin Lipidol. 2015:9;758-769: ODYSSEY ALTERNATIVE
- Kereiakes et al. Am Heart J. 2015:169;906-15: COMBO I
- El Shahawy et al. Am J Cardiol. 2017:120;931-939: COMBO II
- Robinson et al. N Engl J Med. 2015:372;1489-99: ODYSSEY LONG TERM

4.22. The Subcommittee considered that the incidence of any adverse events (AEs) reported in ODYSSEY OUTCOMES was similar between the two treatment groups, with AEs occurring in 75.8% of patients in the alirocumab group compared to 77.1% of the placebo group. The Subcommittee noted that 3.6% of AEs occurring in patients in the alirocumab group led to treatment discontinuation, compared to 3.4% in the placebo group.

4.23. The Subcommittee considered that the most commonly reported AEs leading to discontinuation of alirocumab across all previously mentioned trials were upper respiratory tract symptoms, pruritis and injection-site reactions. The Subcommittee noted that some patients developed antibodies to alirocumab, experienced confusion or memory impairment, or had musculoskeletal or ophthalmological AEs, although the significance of these was unknown and they were not considered to represent safety signals. The Subcommittee considered that AEs of lipid membranes (eg eyes and lips) could occur due to the binding of alirocumab to PCSK9, however the overall safety profile of alirocumab appeared to be acceptable.

4.24. The Subcommittee noted the pooled data from 5,234 patients in four phase II ODYSSEY trials and ten phase III ODYSSEY trials, which reported that treatment-emergent AEs, serious AEs, deaths and treatment discontinuations had similar incidence in the alirocumab groups and the control groups (Leiter et al. Diabet Med. 2018. 35:1742-51). The Subcommittee noted that the authors reported incidence of adjudicated major adverse cardiac events (MACE) from the phase III trial data, stating that MACE occurred in 2.7% of alirocumab-treated patients with diabetes compared to 1.8% of patients without diabetes, and that there was a higher incidence of serious AEs in patients with diabetes.

4.25. Members considered that it was somewhat unclear what benefit alirocumab would provide for patients with HeFH because the primary evidence was applicable to the broader population of patients with hypercholesterolaemia and a recent history of ACS; however, the Subcommittee considered that it was likely that there would be a benefit in terms of CV outcome for patients with HeFH due to a reduction in LDL-C.

4.26. The Subcommittee considered that the evidence demonstrated efficacy of alirocumab in lowering LDL-C with a good safety profile. The Subcommittee considered that the evidence could have been more mature, but that it demonstrated clinical improvement and efficacy of outcome from alirocumab in patients with ACS, and there was reduction in LDL-C and pathophysiological changes in patients with HeFH. Members considered that no data are available in patients with severe hepatic or renal disease, or in pregnancy and lactation.

4.27. The Subcommittee considered that LDL-C is a useful marker of high-cardiovascular risk status and that a reduction in LDL-C is generally expected to convey a benefit in CV outcome for patients with hypercholesterolaemia. However, some members considered a reduction in LDL-C does not always translate to a clinical benefit. The Subcommittee considered that the risk of CV events cannot be completely removed,

and that LDL cholesterol may not be adequately controlled, even with intensive cholesterol-lowering therapy and a high level of treatment compliance.

4.28. The Subcommittee noted that alirocumab is injected subcutaneously every two weeks or every four weeks, and that Medsafe has given approval for both the 75 mg/mL and 150 mg/mL dose forms of alirocumab (Praluent). The Subcommittee noted that the half-life of alirocumab is reduced by concomitant statin use.

4.29. The Subcommittee considered that self-injection of alirocumab was suitable for the proposed patient groups and that it was unlikely that these patients or their caregivers would experience administration issues. The Subcommittee considered that some patients (e.g. some diabetics using insulin) would already be competent with self-injected treatment.

4.30. The Subcommittee noted the proposed dosing regimens of alirocumab are 75 mg fortnightly, 150 mg fortnightly and 300 mg every four weeks. The Subcommittee considered that if alirocumab was funded in NZ, patients would be likely to have high baseline LDL-C, requiring the higher starting dose of alirocumab 150 mg fortnightly in order to achieve maximum improvement in LDL-C. The Subcommittee noted there was limited clinical trial evidence for the 300 mg dosing regimen therefore this would be unlikely to be used in practice.

4.31. The Subcommittee considered that up- or down-titration of alirocumab would not be required because the highest dose would be in use and it is unlikely that LDL-C levels would decrease enough to reduce the dose. The Subcommittee considered that it was difficult to confirm a therapeutic LDL-C goal because it is unlikely that patients would achieve the LDL-C reduction to less than 1.8 mmol/L as seen in the primary clinical trial.

4.32. The Subcommittee considered that treatment with alirocumab was unlikely to create any significant changes in health-sector expenditure other than for direct treatment costs, and that it could reduce health care resource costs by reducing the number of CV events.

4.33. The Subcommittee supported the use of alirocumab for the high-risk and high-need group of patients with HeFH and considered that the applicant proposed that this treatment would be used for primary prevention for patients with HeFH without a prior cardiovascular event.

4.34. The Subcommittee considered that alirocumab would provide a benefit for patients with ACS with diabetes, and that this large, growing, high-risk population would need to be treated for many years to benefit from alirocumab. The Subcommittee considered that CV events would still occur due to the influence of other factors, despite ongoing treatment and adherence. The Subcommittee considered that the subgroups of patients with ACS and diabetes who would be most likely to benefit, and who had the highest health need, would be those patients intolerant to statins and those patients with very high LDL-C despite maximum doses of statins.

5. Tafamidis for cardiac amyloidosis

Application

5.1. The Subcommittee reviewed a clinician application for tafamidis for the treatment of cardiac amyloidosis. The Subcommittee considered that this application was for the treatment of cardiac amyloidosis that is specifically caused by transthyretin

amyloidosis (ATTR). The Subcommittee noted that there had been no contact with the supplier of tafamidis about this product or the current application.

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

Recommendation

5.3. The Subcommittee **recommended** that tafamidis for the treatment of cardiac amyloidosis be funded with a medium priority based on high health need, the lack of funded pharmaceutical alternatives that modify disease progression and a high cost of treatment. The Subcommittee recommended funding with the following restrictions:

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

14. Patient has mutated or wild-type ATTR (transthyretin) amyloidosis; and
15. Patient has histological confirmation of ATTR based on cardiac or non-cardiac biopsy; and
16. Patient has end-diastolic interventricular septal wall thickness of greater than 12 mm on echocardiography; and
17. Either:
    4.1. Patient has been hospitalised for heart failure; or
    4.2. Patient has clinical evidence of heart failure (without hospitalisation) requiring treatment with a diuretic; and
18. Patient's symptoms meet the criteria of the New York Heart Association (NYHA) Class I or II; and
19. Patient has an NT-proBNP of greater than 70 pmol/L; and
20. Patient has not received a liver or heart transplant, or implanted cardiac mechanical assist device.

Note: Patient must not use doxycycline, verapamil or diltiazem during treatment with tafamidis
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:

5. The treatment remains appropriate and the patient is benefiting from treatment; and
6. Patient's symptoms meet the criteria of the New York Heart Association (NYHA) Class I or II; and
7. Patient has an NT-proBNP of greater than 70 pmol/L; and
8. Patient has not received a liver or heart transplant, or implanted cardiac mechanical assist device.

Note: Patient must not use doxycycline, verapamil or diltiazem during treatment with tafamidis.

5.4. The Subcommittee **recommended** that PHARMAC engage with Pfizer, the supplier of tafamidis, following the Subcommittee's positive recommendation.

5.5. The Subcommittee considered that the Rare Disorders Subcommittee of PTAC could review the Subcommittee's minutes regarding this application, for their information.

Discussion

5.6. The Subcommittee noted that amyloidosis is a group of diseases in which abnormal or excessive amyloid (fibril) deposits accumulate in organs, causing rapid progressive damage which is most significant when the heart, kidney, liver and

autonomic nervous system are affected. The Subcommittee considered that patients with amyloidosis have high health need due to this severe, chronic disease which causes poor health and results in an expected survival of between three and five years from diagnosis.

5.7. The Subcommittee noted that abnormal transthyretin (TTR) protein causes the rare condition of transthyretin amyloidosis (ATTR) which can be due to either mutated ATTR (ATTRm) or wild-type ATTR (ATTRwt). The Subcommittee noted that the severity of cardiomyopathy and age of onset can vary in patients with ATTRm, and that patients with ATTRwt typically present between 60 to 70 years of age whereas earlier presentation is likely with ATTRm.

5.8. The Subcommittee noted that although there is no ethnicity data for incidence of ATTR in New Zealand or Australia, certain types of amyloidosis can disproportionately affect indigenous populations, with higher incidence than non-indigenous populations. The Subcommittee considered that there is a health impact on family members of patients with cardiac amyloidosis due to the patient's heart disease, symptoms (including shortness of breath) and dependence.

5.9. The Subcommittee considered that the application was for patients with cardiac amyloidosis that is specifically caused by ATTR, herein referred to as TTR cardiac amyloidosis.

5.10. The Subcommittee considered that in practice, TTR cardiac amyloidosis is difficult to diagnose as there are no overt characteristics other than heart failure or cardiac wall thickening; and, cardiac changes can be misinterpreted as being due to other causes of hypertension. The Subcommittee considered that in New Zealand, patients with TTR cardiac amyloidosis are commonly diagnosed once they reach a New York Heart Association (NYHA) functional classification of III or above because specific investigations commence upon symptomatic presentation.

5.11. The Subcommittee considered that there may be about 50 to 100 patients with TTR cardiac amyloidosis in NZ with a further 10 patients diagnosed per year. However, the exact number is uncertain, with these estimates based on the limited data of amyloidosis prevalence. It was considered that patient numbers may increase over time with an aging population. The Subcommittee considered that this disease would currently meet the PHARMAC Rare Disorders criteria.

5.12. The Subcommittee noted that current treatment is unable to modify the disease course and that no curative treatment is available. The Subcommittee noted that some patients receive a liver or heart transplant, or both, but that amyloid can keep accumulating, and that patients over 60 years of age are generally considered unsuitable for transplant.

5.13. The Subcommittee noted that the application requests funding of tafamidis meglumine (herein referred to as tafamidis), a specific stabiliser of TTR which works to prevent transthyretin from breaking up and forming amyloid deposits. The Subcommittee noted that the applicant has proposed tafamidis be administered orally at a dose of 20 mg per day.

5.14. The Subcommittee noted the primary evidence for tafamidis in TTR cardiac amyloidosis comes from the randomised, phase III, double-blind, placebo-controlled ATTR-ACT trial which investigated the use of 80 mg and 20 mg tafamidis compared to placebo for 30 months in 441 patients with biopsy-confirmed ATTRwt or ATTRm and confirmed cardiac involvement (Maurer et al. N Engl J Med. 2018. 379: 1007-

16). The Subcommittee noted that the ATTR-ACT trial was conducted mainly through specialist medical centres and enrolled about three or four patients with ATTRwt for each patient with ATTRm.

5.15. The Subcommittee noted that the ATTR-ACT trial results pooled the data for the 20 mg and 80 mg doses of tafamidis. The Subcommittee considered that the data suggest that the 20 mg dose provided a similar health benefit to the 80 mg dose, albeit with some uncertainty around this because of small patient numbers.

5.16. The Subcommittee noted that the authors of the ATTR-ACT trial reported all-cause mortality of 29.5% for tafamidis patients compared to 42.9% for placebo patients (HR 0.70, 95% CI 0.51 to 0.96).

5.17. The Subcommittee noted that 52.3% of tafamidis patients in the ATTR-ACT trial had cardiovascular(CV)-related hospitalisations compared to 60.5% of placebo patients, also reported as 0.48 CV-related hospitalisations per year for tafamidis patients compared to 0.70 per year for placebo patients (relative risk ratio 0.68, 95% CI 0.56 to 0.81). The Subcommittee noted that there were higher rates of CV-related hospitalisations with tafamidis than placebo in patients with NYHA class III at baseline.

5.18. The Subcommittee noted that the ATTR-ACT trial reported a quality of life (QoL) benefit, demonstrated by a reduced decline in QoL score with tafamidis compared to placebo, and that there was a benefit of tafamidis with regard to the six-minute walk test as demonstrated by a reduced decline in the six-minute walk test with tafamidis compared to placebo.

5.19. The Subcommittee considered the safety profile of tafamidis was acceptable and supported by robust evidence. The ATTR-ACT trial reported similar incidence of treatment-emergent serious adverse events (SAEs), with at least one treatment-emergent SAE occurring in 75.4% of tafamidis patients compared to 79.1% of placebo patients.

5.20. The Subcommittee considered that the group of patients who received the greatest benefit from tafamidis were those with very early heart failure and only mild or moderate symptoms, who would meet the NYHA class I or II criteria. The Subcommittee considered that there would be less benefit for patients with progressed disease, where a patient may be breathless and have symptoms meeting NYHA class III criteria, noting the higher rate of CV-related hospitalisation in baseline NYHA class III patients as mentioned previously.

5.21. The Subcommittee considered that the ATTR-ACT trial provided good quality evidence for a disease-modifying treatment for patients with TTR cardiac amyloidosis and considered that it was a large study for a rare condition. Members considered that tafamidis had demonstrated efficacy in delaying disease progression and prolonging life, but that the disease would continue despite treatment and tafamidis does not provide a cure. Members considered that it is likely that there would be long-term follow-up studies from within this cohort of patients and that these would provide data on whether the effects are sustained long-term.

5.22. The Subcommittee also noted the following evidence which consists of open-label trials, post-hoc analyses, observational studies and case studies which all investigate the use of tafamidis in TTR cardiac amyloidosis:

- Maurer et al (Circ Heart Fail. 2015. 8: 519-26)

- Sultan et al (Clin Med Insights Cardiol. 2017. 11:1179546817730322)
- Merlini et al (J Cardiovasc Transl Res. 2013. 6: 111-20)
- Damy et al (J Cardiovasc Transl Res. 2015. 8: 117-27)
- Cortese et al (J Neurol. 2016. 263: 916-24)
- Fujita et al (Cardiology. 2017. 137: 74-77)

5.23. The Subcommittee considered that tafamidis appeared to be a suitable treatment for patients with TTR cardiac amyloidosis with NYHA class II disease or below, and that tafamidis would likely be administered for approximately three to five years. The Subcommittee considered that treatment would likely provide a health benefit for family and carers, as it may delay dependence on family and carers.

5.24. The Subcommittee noted that tafamidis is not registered by Medsafe and that no application for tafamidis has been received by Medsafe.

5.25. The Subcommittee noted that the funding application estimated the cost of tafamidis at $650 per 20 mg capsule, equivalent to about $240,000 per annum for 20 mg tafamidis per day. The Subcommittee considered that this cost was very high. The Subcommittee considered that tafamidis would be used as an adjunct to existing treatments (used for symptom control). The Subcommittee noted that tafamidis can also be used for the treatment of amyloid neuropathy but that the application was limited to information regarding ATTR. The Subcommittee noted that other agents are in development for treatment of ATTR and considered that data regarding these agents would be forthcoming.

5.26. The Subcommittee considered that tafamidis may impact on health system resources due to increased screening for TTR cardiac amyloidosis which would involve an echocardiogram (ECHO), magnetic resonance imaging (MRI), and biopsy. The Subcommittee considered that an echocardiogram (ECHO) may reveal suggestive changes and if this diagnosis is considered, it would prompt for definitive assessments using cardiac MRI and biopsy. The Subcommittee considered that biopsy is a costly procedure and requires a specific request to consider a diagnosis of TTR cardiac amyloidosis, however, it was reasonable to require histological confirmation of disease based upon either cardiac or non-cardiac biopsy, before commencing treatment.

5.27. Members considered that technetium-labelled bone scintigraphy has been shown to be a very accurate means of making a diagnosis and could perhaps assist with making early diagnosis.

5.28. The Subcommittee considered that tafamidis may prolong life and that there may be savings to the health system from a reduction in hospital admissions. The Subcommittee considered that it was unclear whether tafamidis would lead to a reduced need for heart or liver transplants.

6. Eplerenone – widening access

Application

6.1. The Subcommittee reviewed applications to widen access to eplerenone to the following patient groups:

- Patients with heart failure and diabetes (or who are at risk of diabetes)
- Patients with primary aldosteronism who are intolerant of spironolactone
- Patients with resistant hypertension who are intolerant of spironolactone

Recommendation

6.2. The Subcommittee **recommended** that the application to widen access to eplerenone for patients with heart failure and diabetes, or heart failure with risk of diabetes, be declined. The Subcommittee recommended this because the SNOW trial showed that eplerenone would not in this group provide any additional benefits compared with spironolactone.

6.3. The Subcommittee **recommended** widening access to eplerenone for patients with primary aldosteronism who are also intolerant of spironolactone with a high priority. The Subcommittee considered there was a lack of alternative treatments for this patient group, and that studies demonstrated eplerenone would help with this condition.

6.4. The Subcommittee **recommended** widening access to eplerenone for patients with resistant hypertension who are also intolerant of spironolactone with a medium priority. The Subcommittee considered that this patient group had few effective treatments and there was generally evidence that eplerenone could treat hypertension.

Discussion

6.5. The Subcommittee noted that eplerenone had been funded under Special Authority criteria since July 2018, and that a number of funding applications had since been received seeking wider access than the group currently funded.

Patients with heart failure, and with diabetes or risk of diabetes

6.6. The Subcommittee noted that it had reviewed the evidence for eplerenone in this patient group at it meeting of February 2016, and it had deferred making a decision until the publication of the SNOW trial. The Subcommittee noted that PTAC has also reviewed the same evidence in November 2015, August 2016, and May 2017, and that PTAC shared the same view.

6.7. The Subcommittee noted that the SNOW trial (Korol et al Am Heart J 2018;0:1-6) was a trial of 62 patients with heart failure (left ventricular ejection fraction less than 40%) who also have type II diabetes or glucose intolerance. These patients were randomised to receive either spironolactone or eplerenone. The Subcommittee noted that the study reported no statically significant difference in change of HbA1c between the two groups, and also reported no statistically significant difference in any of the eight secondary endpoints.

6.8. The Subcommittee considered that in this patient group, based on the results of the SNOW trial and the evidence previously considered, eplerenone has similar efficacy to spironolactone and so offered no advantage to patients in this group if they are able to take spironolactone. The Subcommittee also noted that patients intolerant to spironolactone can already access eplerenone under the current Special Authority criteria.

Patients with primary aldosteronism who are also intolerant of spironolactone

6.9. The Subcommittee reviewed an application to widen access to eplerenone for primary aldosteronism (also called Conn's syndrome) where the patient is intolerant of spironolactone.

6.10. The Subcommittee estimated that under 100 new patients would likely meet this criteria each year, though noted the exact number was uncertain. Members considered that this condition was underdiagnosed. The Subcommittee considered that there was a lack of funded treatments for this condition given that these patients are intolerant to spironolactone, and given the recent discontinuation of amiloride tablets.

6.11. The Subcommittee reviewed the evidence cited for eplerenone in primary aldosteronism, and considered the primary evidence to be from two trials reported by Parthasarathy et al (Journal of Hypertension 2011, 29:980-990) and Karagiannis et al (Expert Opin. Pharmacother. 2008, 9(4):509-515).

6.12. Parthasarathy et al conducted a randomised controlled trial of 141 patients with primary aldosteronism who received either eplerenone or spironolactone for 16 weeks. The Subcommittee considered the results of the trial and noted that patients administered spironolactone had a statistically significant greater reduction in diastolic blood pressure than patients administered eplerenone. However, the Subcommittee considered that eplerenone did reduce diastolic blood pressure; this was reduced by 5.6 ± 1.3 mmHg compared with baseline measurements before the start of the trial.

6.13. Karagiannis et al conducted an open-label trial which included patients with primary aldosteronism, as well as patients with bilateral idiopathic hyperaldosteronism. There were 34 patients randomised to eplerenone or spironolactone. The primary outcome was having blood pressure below 140/90 mmHg at week 16 of the trial. The authors of the paper reported that 76% of spironolactone patients and 82% of patients administered eplerenone met the primary outcome (13 out of 17 vs 14 out of 17, p = 1.000).

6.14. The Subcommittee noted that the trials provided only surrogate data. The Subcommittee considered that eplerenone is likely to be either as effective or less effective than spironolactone. The Subcommittee considered there was sufficient evidence to indicate that eplerenone provided some benefit compared with no treatment. The Subcommittee considered that based on this, eplerenone would be an appropriate treatment to trial in a patient unable to tolerate spironolactone.

6.15. The Subcommittee considered that the Special Authority would need to include a definition of primary aldosteronism, that is, a verifiable test result. The Subcommittee considered that it would be appropriate to use the same text for "intolerant of spironolactone" as is currently used for the heart failure indication.

Patients with resistant hypertension who are intolerant to spironolactone

6.16. The Subcommittee reviewed an application to widen access to eplerenone for patients with resistant hypertension (defined as high blood pressure despite being on three agents at once, including a diuretic if possible) where the patient is intolerant of spironolactone.

6.17. The Subcommittee considered this was a more difficult group to define and that there could be a large number of patients, potentially several thousand.

6.18. Members considered that if funded in this setting, eplerenone would be taken concurrently with other medicines. If treatment is effective it could lead to stopping some antihypertensive treatments.

6.19. The Subcommittee considered a Cochrane meta-analysis of eplerenone in primary hypertension (Cochrane Database Syst Rev. 2017 Feb 28;2:CD008996). This analysis combined five studies of a total of 1437 patients. Based on the meta-analysis, the Cochrane authors reported that eplerenone provides a reduction in systolic blood pressure of around 9 mmHg and a reduction of diastolic blood pressure of around 4 mmHg. The authors of the paper concluded there was moderate quality evidence to support these outcomes, but noted the studies did not have data on mortality, myocardial infarction, and stroke.

6.20. The Subcommittee considered that the studies and the meta-analysis provided sufficient evidence that eplerenone would be a useful treatment for resistant hypertension.

6.21. The Subcommittee considered that any Special Authority would need to be very clearly defined, including requiring that patients are resistant to treatment with at least three antihypertensives and are intolerant to spironolactone.

7. Pulmonary arterial hypertension treatments – widening access to funded medicines

Application

7.1. The Subcommittee reviewed a number of proposed changes to the funding criteria and funding process for pulmonary arterial hypertension (PAH) treatments.

Recommendation

7.2. The Subcommittee **recommended** widening access to sildenafil for PAH as follows, with a low priority (additions in bold, deletions in strikethrough):

Initial application — (Pulmonary arterial hypertension*) only from a respiratory specialist, cardiologist or medical practitioner on the recommendation of a respiratory specialist or cardiologist. Approvals valid without further renewal unless notified for applications meeting the following criteria:

All of the following:
1 Patient has pulmonary arterial hypertension (PAH)*; and
2 Any of the following:
- 2.1 PAH is in Group 1 of the WHO (Venice) clinical classifications; or
- 2.2 PAH is in Group 4 of the WHO (Venice) clinical classifications; or
- 2.3 PAH is in Group 5 of the WHO (Venice) clinical classifications; and

~~3 Any of the following:~~
- ~~3.1 PAH is in NYHA/WHO functional class II; or~~
- ~~3.2 PAH is in NYHA/WHO functional class III; or~~
- ~~3.3 PAH is in NYHA/WHO functional class IV; and~~

~~4~~ Either:
- 4.1 All of the following:
  - 4.1.1 Patient has a pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mmHg; and
  - 4.1.2 Either:
    - 4.1.2.1 Patient has a mean pulmonary artery pressure (PAPm) > 25 mmHg; or

4.1.2.2 Patient is peri Fontan repair; and

4.1.3 Patient has a pulmonary vascular resistance (PVR) of at least 3 Wood Units or at least 240 International Units (dyn s cm-5); or

4.2 Testing for PCWP, PAPm, or PVR cannot be performed due to the patient's young age.

Note: Indications marked with * are unapproved indications

The Subcommittee considered that the criteria proposed for deletion above either are not limiting access, so are unnecessary, or are not required given sildenafil's low cost.

7.3. The Subcommittee **recommended** widening access to medicines for PAH to allow first-line dual therapy (that is, to remove the requirement to trial a monotherapy) with a high priority. Members considered that there was evidence to support first-line dual therapy in general.

7.4. The Subcommittee **recommended** that PTAC approach suppliers of tadalafil, as there is better evidence for tadalafil and for sildenafil in some treatment pathways.

Discussion

7.5. The Subcommittee noted that the last substantial changes to criteria for PAH medicines had been made in February 2018. The Subcommittee considered that the current criteria for accessing PAH medicines, particularly the PAH Panel forms, remained confusing. Members noted that these forms used the word "may" a lot, leaving obligations unclear, and referred to "rapid" as well, a term which was not clearly defined.

Sildenafil criteria

7.6. The Subcommittee discussed the funding criteria for sildenafil. The Subcommittee noted that since moving sildenafil from a Panel application to a standard Special Authority form, there had been a number of waiver requests, mostly for children unable to have certain tests performed. The Subcommittee considered possible simplifications to the criteria that would mean clinicians would no longer need to report certain test results.

Sildenafil criteria – Type of PH (WHO classification)

7.7. The Subcommittee considered that targeting funded access to patients in Group 1, 4, or 5 of the WHO (Venice) classifications (current criteria 2) remained appropriate. The Subcommittee considered that there was no evidence for sildenafil in Groups 2 and 3. The Subcommittee discussed how much extra use of sildenafil there would be if restrictions to specific WHO classifications were removed. The Subcommittee considered that "patients with PH (Groups 2 and 3)" is a large patient group of around 15,000 patients in New Zealand. However, members considered that since there is no evidence that these patients would benefit from sildenafil, uptake would likely be low.

Sildenafil criteria – Severity (NYHA/WHO functional classes)

7.8. The Subcommittee considered that there was no clinical need for a criterion restricting to NYHA/WHO functional class II or worse, as patients with PAH are generally not diagnosed with the condition until they reach the severity of functional class II at least.

Sildenafil criteria – Diagnostic tests (right heart catheterisation)

7.9. Members noted that current criterion 4 of the Special Authority requires patients to have undergone the right heart catheterisation (RHC) test, and to report results which demonstrate PAH. The Subcommittee considered that all patients should have RHC done to confirm the diagnosis of PAH, and considered it should remain best practice. Members discussed whether it was the role of the Special Authority to enforce best practice, noting that funding for other medicines leave it to the clinician to ensure appropriate diagnosis. Other members considered that there was value in ensuring RHC had been done wherever possible as diagnosis of PAH without RHC was often inaccurate.

7.10. Members considered that there can be difficulties for some patients in accessing RHC as this procedure requires referral to a major center.

7.11. Members considered that there would be no immediate harm from providing sildenafil to a patient with left heart PH (Group 2 or 3), and that the cost would be low. However, members also considered that sildenafil would give no benefit in this patient group. Members also considered that this approach could lead to harm; if patients were assumed to have PAH then they would not receive treatment appropriate for PH. Patients could also progress through PAH treatments, and there is evidence that bosentan is actively harmful to a patient with left heart PH.

7.12. Members noted that the cost of sildenafil had significantly decreased. Members considered that it may be more appropriate to require RHC as proof of PAH for funding of more expensive medicines, to ensure that these expensive treatments continue to be targeted to those most likely to benefit.

7.13. Members discussed allowing sildenafil for a fixed period, to allow early treatment before a patient is old enough for an RHC. Members also speculated that since sildenafil is ineffective in left heart PH, that if sildenafil led to improvement of the condition this could be evidence that the condition is PAH. However, Members considered that there could also be a ‘placebo-like’ effect in this circumstance, which could lead to an incorrect diagnosis.

7.14. The Subcommittee did not reach a consensus on whether or not the requirement for haemodynamic evidence of pulmonary hypertension in the form of a right heart catheter should be removed from the Special Authority.

First-line dual therapy

7.15. The Subcommittee reviewed the 2015 ESC/ESR guidelines, and in particular its recommendations around combination therapy. The Subcommittee noted that these guidelines recommended a number of dual therapy treatments at first-line. The Subcommittee noted that currently, dual therapy is only funded after a trial of monotherapy. The Subcommittee considered that it was international practice to use first-line dual therapy, and that this was supported by evidence indicating a benefit from use of first-line dual therapy above that of single therapy. The Subcommittee considered that it was important to treat patients with PAH early with the most effective treatment paradigm (first-line dual therapy) to help reduce progression of the disease.

7.16. The Subcommittee in particular reviewed a citation from the guidelines, Galiè et al 2015 N Engl J Med 2015; 373:834-844 (the AMBITION trial), which compared ambrisentan with tadalafil against ambrisentan only and tadalafil only. Members

considered that this trial was typical of studies for PAH, in that patient numbers were not large, and the primary outcome was time taken to clinical worsening rather than clinical improvement.

7.17. The Subcommittee noted that Galiè et al was a randomised controlled double-blind trial in which the 500 treatment naive patients were randomised to receive ambrisentan, tadalafil, or the combination of both. The primary outcome was time to "clinical failure" a composite endpoint met if the patient had any of the following within 24 weeks: death, hospitalisation for worsening PAH, disease progression, or unsatisfactory long-term clinical response. Each of these outcomes was defined by specific measures. The study reported that 18% of patients met the primary endpoint with the combination, compared with 25% with tadalafil only and 34% with ambrisentan only (Hazard Ratio for combination vs tadalafil: 0.53, 95% CI 0.34-0.83). The Subcommittee considered that these differences were clinically meaningful.

7.18. The Subcommittee considered that this evidence was of reasonable quality. The Subcommittee also considered that the ESC/ESR guidelines generally presented reasonable evidence that first-line dual therapy was appropriate. The Subcommittee also noted the latest CHEST guidelines of 2019 from the USA which also supported first-line dual therapy.

7.19. In comparison, the Subcommittee considered McLaughlan et al (Eur Respir J. 2015;46(2):405-413) which investigated sequential therapy, similar to the currently funded treatment paradigm, in which bosentan was added to symptomatic but stable PAH patients on sildenafil. The Subcommittee considered that although the authors of the study reported a benefit regards to the 6-minute walk test, adding bosentan to stable sildenafil therapy was not superior to sildenafil monotherapy in delaying the time to the first morbidity/mortality event. paradigm the benefits were unlikely to be clinically meaningful.

7.20. Arising from this discussion, the Subcommittee considered tadalafil. The Subcommittee considered that there was better evidence for dual therapies that involved tadalafil than there was for those with sildenafil. The Subcommittee also noted that there was a Medsafe-registered supplier of tadalafil, and that it was taken once a day instead of three times a day for sildenafil. The Subcommittee considered that PHARMAC should approach suppliers of tadalafil.

7.21. The Subcommittee considered that if access to PAH treatments was widened to include dual first-line therapy that the Special Authority criteria requiring right heath catheterisation would be needed for the reasons previously discussed (described above in paragraphs 9.11 and 9.12).

PAH Panel

7.22. The Subcommittee noted that from February 2018, funded access to sildenafil and bosentan was changed from a special access Panel to a standard Special Authority, and the Subcommittee reviewed data on how this change affected use of these medicines. The Subcommittee also reviewed data on the PAH Panel and information on how it assesses applications.

7.23. The Subcommittee considered that usage of sildenafil and bosentan had not substantially risen since being moved to a Special Authority. The Subcommittee also noted that the PAH Panel approves about 95% of the applications it receives.

7.24. The Subcommittee considered that there would be no clinical benefits in removing the special access Panel for ambrisentan, iloprost, and epoprostenol. The Subcommittee also considered that the Panel has value in providing advice to the clinicians who make applications, as well as advising PHARMAC on PAH matters.