Cardiovascular Subcommittee of PTAC
Meeting held 17 February 2016

(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 were reviewed by PTAC at its meeting on 11 & 12 August 2016.

Record of the Cardiovascular Subcommittee of PTAC meeting held on 17 February 2016

Previous recommendations and action points

3.1. The Subcommittee noted that in November 2015, PTAC recommended that idarucizumab be listed in Section H of the Pharmaceutical Schedule for the specific reversal of the anticoagulant effects of dabigatran when required in situations of life-threatening or uncontrolled bleeding, or for emergency surgery or urgent procedures, with a medium priority.

3.2. The Subcommittee considered that if another NOAC was listed, a considerable number of patents are likely to remain on dabigatran, and therefore an antidote would remain useful.

3.3. The Subcommittee noted that the RE-VERSE AD trial of idarucizumab was underway with New Zealand, having enrolled approximately 30% of patients. Members considered the results published by the interim analysis indicated that idarucizumab was very effective at reversing the effects of dabigatran. The Subcommittee noted that some patients in the trial required a second dose of idarucizumab.

3.4. The Subcommittee considered that usage of idarucizumab might be substantial if not carefully controlled. Members considered that idarucizumab should be used under haematologist guidance to enable use to be targeted to clinically urgent situations.

3.5. Members considered that idarucizumab was likely to be expensive, but felt that it would be less expensive overall when compared to the use of alternatives including blood products which are also expensive and sometimes ineffective.

1. Eplerenone

Application

1.1. The Subcommittee reviewed an application for eplerenone in heart failure patients with an ejection fraction of less than or equal to 40% and diabetes, or with a high risk of diabetes, and an application for patients with heart failure who are intolerant to optimal dosing of spironolactone.

Recommendation

1.2. The Subcommittee **recommended** that eplerenone be funded with a high priority on the Pharmaceutical Schedule in heart failure patients with an ejection fraction of less than 40%, and who are intolerant to optimal dosing of spironolactone due to severe disabling mastalgia, via a Special Authority.

1.3. The Subcommittee considered that results for a clinical trial in Montreal, Comparison of Eplerenone versus Spironolactone in Heart Failure Patients With Glucose Intolerance or Type 2 Diabetes (SNOW), were due to be available in June 2016. The Subcommittee deferred making a recommendation about funding eplerenone for indications relating to diabetes until the results of the SNOW trial are available.

Discussion

1.4. The Subcommittee noted that PHARMAC staff had received an application from Te Arai BioFarma that had been considered by PTAC at its November 2015 meeting. It noted that PTAC has made the following recommendations in relation to eplerenone:

1) PTAC recommended that eplerenone for patients with an ejection fraction of less than or equal to 40% and diabetes, or with a high risk of diabetes, be declined.

2) PTAC recommended that eplerenone be funded on the Pharmaceutical Schedule for patients with heart failure who are intolerant to optimal dosing of spironolactone with a low priority.

1.5. The Subcommittee noted that PTAC requested that the Cardiovascular Subcommittee review the application to examine the strength of the evidence and to determine appropriate Special Authority (SA) criteria/hospital restrictions.

1.6. The Subcommittee considered that the evidence in the application was of good quality; however, the Subcommittee considered that the evidence provided did not support use in the indications requested in the application. Members considered that there was no current evidence that strongly supported the addition of diabetes to the indication for use.

1.7. Members considered that due to the necessity of extrapolating from the evidence provided to reach conclusions relevant to the application, the overall quality of the evidence to support the application was weak to moderate.

1.8. The Subcommittee considered that some patients experienced gynaecomastia with mastalgia as a side effect of spironolactone to varying degrees. The Subcommittee considered that the incidence of patients experiencing disabling mastalgia was between 1-2% of patients taking spironolactone (RALES study, Pitt et al. N Engl J Med 1999:341:709-17.). Members considered that the gynaecomastia was reversible if recognised within 6 months of starting spironolactone, but could become chronic if not recognised and treatment stopped within that timeframe. The Subcommittee considered that mastalgia as an adverse effect of spironolactone was experienced equally by both females and males. The Subcommittee considered that around 5% of patients would discontinue treatment with spironolactone if they experienced either mastalgia or gynaecomastia.

1.9. The Subcommittee considered that access to eplerenone for patients who were intolerant to optimal dosing of spironolactone should be via a Special Authority. The Subcommittee considered that this intolerant group would only include patients who developed severe disabling mastalgia. As such, a Special Authority would restrict treatment with eplerenone to patients who experienced severe disabling mastalgia while taking spironolactone. Members considered that this would prevent large numbers of patients changing heart failure treatment (from spironolactone to eplerenone) for other indications. Members considered that patients with stable heart failure while on spironolactone, who are not experiencing intolerably painful mastalgia, would not actively make the switch to eplerenone.

1.10. The Subcommittee considered it would be possible to restrict eplerenone to patients who were intolerant to spironolactone and who had a specified left ventricular ejection fraction that had been confirmed by echocardiogram. Members considered

that patients who had heart failure of that severity would have undergone an echocardiogram as part of routine diagnostic testing.

1.11. The Subcommittee noted that there are approximately 26,000 patients in New Zealand on spironolactone (out of 350,000 to 400,000 patients being treated for heart failure), and agreed with PHARMAC's estimate that around 1 to 2 percent of these patients on spironolactone would experience side effects considered intolerable such that they would switch to eplerenone if funded.

1.12. The Subcommittee considered that a Special Authority that restricts eplerenone to patients with heart failure who experience mastalgia while taking spironalactone would allow a high recommendation for funding to be made.

1.13. The Subcommittee considered that results for a clinical trial in Montreal, Comparison of Eplerenone Versus Spironolactone in Heart Failure Patients With Glucose Intolerance or Type 2 Diabetes (SNOW), were due to be available in June 2016. The Subcommittee deferred making a recommendation about funding eplerenone for indications relating to diabetes until the results of the SNOW trial are available.

2. Fixed dose combination polypills

2.1. The Subcommittee noted that PHARMAC staff were requesting clinical advice from the Subcommittee on the wider concepts and acceptability around fixed dose combination pills (FDCs) for the management of cardiovascular risk. The Subcommittee noted that PHARMAC staff had requested that the Cardiovascular Subcommittee provide clinical advice around the opportunities and challenges provided by FDCs, in terms of health outcomes in New Zealand. The Subcommittee considered that a "polypill" was a pill with multiple agents that targeted multiple indications.

2.2. The Subcommittee noted and reviewed the registration status of and the availability of FDC polypills internationally. The Subcommittee noted that there are many dual agent cardiovascular products listed on the Australian PBS, and that these include the following combinations: Angiotensin converting enzyme inhibitors with calcium channel blockers, angiotensin II receptor blockers with calcium channel blockers, calcium channel blockers with statin. The Subcommittee noted that the US FDA has recently approved Entresto (an angiotensin II receptor blocker and neprilysin inhibitor combination). The Subcommittee noted that there are a number of triple agent cardiovascular products listed and that these include: Sevikar HCT (olmesartan, amlodipine, hydrochlorothiazide) (MSD), Exforge HCT (valsartan, amlodipine, hydrochlorothiazide) (Novartis), Amturnide (amlodipide, aliskiren, hydrochrothiazide) (Novartis).

2.3. The Subcommittee noted that there are currently four funded dual agent FDC cardiovascular products on the Pharmaceutical Schedule. These include an angiotension converting enzyme inhibitors with diuretics, angiotensin II receptor blockers with diuretics, ezetimibe with simvastatin, and potassium sparing diuretic combinations.

2.4. The Subcommittee noted that an application had been received from Te Arai Biopharma for the listing of Trinomia 'Polypill' (aspirin 100 mg, atorvastatin 20 mg, and Ramipril 2.5 mg, 5 mg, 10 mg) for the secondary prevention of cardiovascular events. The Subcommittee noted that New Zealand clinicians/public health

physicians had provided support for the concept of fixed dose combination (FDC) products for the prevention of both primary and secondary cardiovascular events.

2.5. The Subcommittee noted the submission from Te Arai Biopharma, including the following publications and randomised control trials:

- Huffman et al. 2012, WHO application.
- Elley et al. Plos one. 2012: 7(12);1-10.
- Wiley & Fuster. Annals Global Health. 2014: 80; 24-34.
- Vila et al. Int J Cardiol. 2014: 177; 209-210.
- FOCUS trial (Castellano et al. J Am Coll Cardiol 2014;64:2071-82.)
- IMPACT trial (Selak et al. BMJ 2014;348:g3318)
- Kanyini GAP trial (Patel et al. Eur J Prev Cardiology. 2015;22(7):920-930., Lea Laba et al. MJA 2014;201(11):671-673.)
- UMPIRE trial (Thom et al. JAMA. 2013;310(9):918-929)

The Subcommittee reviewed the evidence in the Te Arai Biopharma submission and considered this evidence presented to be of low direct relevance to the Trinomia polypill submission.

2.6. The Subcommittee noted the Cochrane review (de Cates et al. 2014. The Cochrane Collaboration.). The Subcommittee considered that the Cochrane review included small trials with end points that were not clinically relevant and that the quality of the evidence was low. The Subcommittee considered that the overall data of these clinical trials showed improved self-reported patient adherence but no significant improvement in clinical outcomes. Members considered that increased adherence was not a proxy for improved direct patient-oriented health outcomes.

2.7. The Subcommittee noted the FOCUS trial (Castellano et al. J Am Coll Cardiol 2014;64:2071-82.), the Kanyini GAP trial (Patel et al. Eur J Prev Cardiology. 2015;22(7):920-930., Lea Laba et al. MJA 2014;201(11):671-673.) and the IMPACT trial (Selak et al. BMJ 2014;348:g3318). The Subcommittee considered these trials to be under powered and of low quality.

2.8. In the IMPACT trial subanalyses (Selak et al., unpublished), the Subcommittee noted that there was an improvement in self-reported adherence in the Māori and Pacific Island populations taking polypills; however, members considered that this did not necessarily reflect a reduction in health inequity. Members considered that polypills attract reduced pharmacy dispensing charges upon receiving only one pill rather than three separate pills, which may influence whether the medication is more likely to be collected from the pharmacy, potentially leading to improved self-reported adherence.

2.9. The Subcommittee noted the following trials of polypills for cardiovascular risk were in progress: HOPE-3, TIPS 3, HOPE-4, PROPS.

2.10. The Subcommittee considered that challenges of use of FDC polypills compared with individual component pills includes difficulty in determining a specific agent responsible for causing an adverse effect, the inability to tailor and titrate treatments to specific patient needs, and the risk of some patients being over-prescribed certain agents due to their presence in a fixed dose combination pill.

2.11. The Subcommittee considered that the convenience of taking one FDC polypill (instead of multiple single pills) would be minimal in those patients who are already taking a number of medications for multiple comorbidities.

2.12. The Subcommittee considered that larger studies evaluating the effect of FDC pills on cardiovascular outcomes, in a community sample similar to the New Zealand population was needed before a recommendation could be made. The Subcommittee also considered that these larger studies should show the same clinical outcomes as the funded alternative treatments, in order to make a recommendation for listing a FDC pill on the Pharmaceutical Schedule.

3. IV Sildenafil

Application

3.1. The Subcommittee noted a clinician's application on behalf of the Paediatric Intensive Care Unit (PICU) at Starship Children's Hospital (Auckland DHB), for listing intravenous sildenafil (Revatio) in Section H of the Pharmaceutical Schedule for the treatment of pulmonary hypertension in patients who are pre or post cardiac surgery, and the treatment of patients with pulmonary hypertension from other causes (e.g. congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn).

Recommendation

3.2. The Subcommittee **recommended** that IV sildenafil be listed in Section H of the Pharmaceutical Schedule of intravenous sildenafil (Revatio) for the treatment of pulmonary hypertension in patients who are pre- or post- cardiac surgery, and the treatment of patients with pulmonary hypertension from other causes (e.g. congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn) with a high priority.

Discussion

3.3. The Subcommittee considered that the evidence provided in the application was of good quality.

3.4. The Subcommittee considered that the alternative for paediatric patients unable to take oral sildenafil was long-term inhaled nitric oxide (NO). Members noted that inhaled NO in Australia was charged on a per minute basis and that this increase in the cost of NO has not occurred in New Zealand. Members considered that patients must be intubated and ventilated to consider the use of NO as an alternative.

3.5. Members considered that the benefits of IV sildenafil for paediatric patients that were unable to take oral sildenafil were that there was no variability in gastrointestinal absorption and intubation was not required (as with inhaled NO). Members considered that IV sildenafil would be used as a bridging treatment post surgically, after which patients could then be started on oral sildenafil.

3.6. The Subcommittee considered that the population who would benefit the most from access to IV sildenafil would be very small, approximately 10 patients per year per PICU, increasing to approximately 50 patients per year if access to IV sildenafil included the neonatal intensive care units (NICU). Members considered that the treatment period per patient would be 48 hours. The Subcommittee considered that it would be appropriate to restrict this treatment to use in the NICU and PICU. The Subcommittee considered that clinicians may want to access this treatment for use in other conditions and considered that, should this be the case, that application forms should be submitted for consideration.

4. Lipid modifying agents

4.1. The Subcommittee noted that at the time of its previous meeting in February 2014, rosuvastatin as a third line statin treatment had been prioritised against PHARMAC's other funding options.

4.2. The Subcommittee noted that the results of the IMPROVE-IT study on ezetimibe, which had not been released in time for its February 2014 meeting, had the potential to provide evidence for the use of ezetimibe as a third-line lipid modifying treatment for patients who were not adequately controlled or could not tolerate other funded options. Members noted that the results from the IMPROVE-IT trial had been presented at the American Heart Association (AHA) 2014 Scientific Sessions and subsequently published in May 2015.

4.3. The Subcommittee considered that the study was robust, but represented older clinical practice using 40 mg simvastatin and that a comparison with contemporary practices could not be drawn from this information. Members considered that the current practice for the reduction of low-density lipoprotein cholesterol (LDL-C) levels was to use higher-dose statins. Members considered that as rosuvastatin is a newer medication and that there have not been as many studies conducted, those which have been conducted have tended to focus on lower risk groups with surrogate outcomes. Members considered that there was currently limited evidence that rosuvastatin may have a role in patients who were intolerant to other statins.

4.4. Members considered that evidence indicates patients not achieving adequate results on atorvastatin improve their LDL-C levels when switched to rosuvastatin (Glueck et al. Clin Ther. 2006 Jun;28(6):933-42).

4.5. The Subcommittee considered that funding for ezetimibe would be appropriate for patients who are intolerant to both atorvastatin and rosuvastatin The Subcommittee noted that these agents are chemically similar although rosuvastatin is more potent. The Subcommittee considered that the current evidence base for lipid modifying agents was in favour of rosuvastatin.

4.6. The Subcommittee considered potential Special Authority criteria for rosuvastatin. The Subcommittee considered that if rosuvastatin was funded, the Special Authority criteria should allow access to patients with total cholesterol levels of >10 mmol/L; and patients who are intolerant to the alternative funded treatments. Members considered that this specific patient group would be small. The Subcommittee considered that if generic rosuvastatin was cost neutral to atorvastatin, it may be appropriate for the criteria for rosuvastatin to include those whose LDL cholesterol is >2.5mmol/L on maximally tolerated doses of atorvastatin.