Cardiovascular Subcommittee of PTAC meeting held 7 June 2012

(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 2008*.

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.
- that any part of the minutes relating to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML) will be released, in a complete publication with the original Hospital Pharmaceuticals Subcommittee minutes and final recommendations made by PTAC, once PTAC have reviewed each therapeutic group.

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 2 & 3 August 2012, the record of which will be available on the PHARMAC website September 2012.

Contents

1 Ranolazine and nicorandil for refractory angina

Application

1.1 The Subcommittee reviewed a memorandum from PHARMAC staff regarding the listing of ranolazine and nicorandil on the Pharmaceutical Schedule for the treatment of refractory angina.

Recommendation

1.2 The Subcommittee **recommended** that an additional treatment for refractory angina should be listed with a high priority, that this should be positioned after maximal treatment with first-line therapies (including beta-blockers, calcium channel antagonists and long-acting nitrates), that this could be either ranolazine or nicorandil (although preferably both), and that both are clinically preferable to perhexiline which should be the last-line product due to its increased monitoring requirements and potential for complications.

The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (iv) The clinical benefits and risks of pharmaceuticals.

Discussion

1.3 The Subcommittee noted that angina treatment includes two components – relieving symptoms of ischaemia and improving outcomes by preventing cardiovascular events and mortality.

1.4 The Subcommittee noted that current first-line treatments include beta-blockers, calcium channel antagonists and long-acting nitrates.

1.5 The Subcommittee noted that perhexiline, nicorandil, ranolazine and ivabradine could potentially be used in patients who are unable to achieve adequate angina symptom control with first-line treatments. The Subcommittee noted that of these only perhexiline is currently funded.

1.6 The Subcommittee noted that non-pharmacological treatments included revascularization, transmyocardial laser revascularization and spinal cord stimulation for patients in whom severe angina is truly refractory.

1.7 The Subcommittee noted the most relevant ranolazine, perhexiline and nicorandil trials for patients with refractory angina are as follows:

Ranolazine

1.8 The Subcommittee noted that in the CARISA (Chaitman et al - CARISA Investigators JAMA. 2004;291(3):309) trial of 823 symptomatic patients with severe chronic angina taking standard doses of atenolol, amlodipine, or diltiazem that after 12 weeks of therapy 750 mg and 1000 mg doses of ranolazine increased exercise capacity (symptom-limited exercise duration increased by 115.6 seconds from baseline in both ranolazine groups

(pooled) vs 91.7 seconds in the placebo group (P =.01)),and provided additional antianginal relief (angina frequency reduced by 0.8 and 1.2 episodes per week compared to placebo; P<0.02).

1.9 The Subcommittee noted that in the ERICA (Stone et al - ERICA Investigators J Am Coll Cardiol. 2006;48(3):566) trial of 565 stable patients with continued anginal attacks despite being treated with the maximum recommended dose of amlodipine that ranolazine significantly reduced the frequency of angina episodes versus placebo (2.88 vs. 3.31; p = 0.028) and nitroglycerin consumption (2.03 vs. 2.68; p = 0.014) versus placebo and the Subcommittee also noted that it was well tolerated.

1.10 The Subcommittee noted that in the MERLIN TIMI 36 (Wilson et al. J Am Coll Cardiol. 2009;53(17):1510) trial of 3565 patients with established coronary artery disease that despite high use of statins and beta-blockers and moderate use of calcium channel blockers and long-acting nitrates, that ranolazine versus placebo was effective in reducing angina (worsening angina was 5.6% v 8.1% p=0.048 and intensification of antianginal therapy was 12.5% vs 16.4% p = 0.005) and recurrent ischemia(16.5% vs 21.1% p=0.002) versus placebo.

Perhexiline

1.11 The Subcommittee noted that while perhexiline reduces the effects of angina, it also has hepatotoxicity and peripheral neuropathy concerns, although the incidence of these complications can be reduced by monitoring and maintaining plasma drug concentrations between 150 and 600 ng/mL.

1.12 The Subcommittee noted a randomized double-blind placebo-controlled crossover trial by Cole et al (Circulation. 1990;81(4):1260) of 17 patients with refractory angina who continued to receive maximal antianginal therapy (typically including nitrates, a beta-blocker, and a calcium channel antagonist) and whose plasma drug levels were monitored and maintained in the 150-600 ng/mL range. The Subcommittee noted that perhexiline improved exercise testing, angina frequency, and anginal severity as well as the patient's perception of improvement. The Subcommittee noted that the side effects observed were minor and related to transient elevations of plasma drug concentration greater than 600 ng/mL.

Nicorandil

1.13 The Subcommittee noted the results of the IONA randomised trial (Lancet. 2002; 359(9314):1269-1275) and a subgroup analysis (Heart. 2004; 90:1427-1430). The Subcommittee noted that the trial investigated the effect of nicorandil (20 mg twice per day) on coronary events in 5126 patients with chronic stable angina who were receiving other standard therapies (antiplatelet drugs 88%, beta blockers 56%, calcium channel blockers 55%, statins 57%, and ACE inhibitors 29%) versus placebo. The Subcommittee noted that after a mean follow-up of 1.6 years nicorandil reduced the composite endpoint of coronary death, nonfatal MI, or unplanned hospitalization for angina (13.1% for nicorandil versus 15.5% for placebo; p=0.014), as well as the incidence of unplanned hospitalization and acute coronary syndrome (6.1% versus 7.6%; p=0.028) with the greatest absolute risk reduction occurring in the third of patients with the highest risk (NNT of 28 versus 46 and 63 for the patients with the middle and lower risk respectively).

Conclusions

1.14 The Subcommittee considered that as there are no head-to-head trials, the relative benefit of ranolazine, perhexiline and nicorandil in refractory patients is difficult to determine. The Subcommittee considered that ideally all three would be available following the first-line therapies; however, it noted that pricing, availability and registration status may impact on this.

1.15 The Subcommittee considered the efficacy of ranolazine and nicorandil to be similar and both are preferable to perhexiline on the basis of its potential for complications and the additional monitoring requirements. The Subcommittee considered that due to the similar efficacy, price would be an important factor in determining the positions of ranolazine and nicorandil in the treatment pathway.

1.16 The Subcommittee recommended that an additional treatment for refractory angina should be listed with a high priority, that this should be positioned after maximal treatment with first-line therapies, that this could be either ranolazine or nicorandil (preferably both), and that both are clinically preferable to perhexiline which should be the last-line product due to its increased monitoring requirements and potential for complications.

1.17 The Subcommittee considered that if another treatment option was available as an alternative to perhexiline then the threshold for its use would be lower than that for perhexiline and as a result the total number of patients may be double that of perhexiline. However the Subcommittee considered that this would result in a reduction in costs associated with angina including reduced clinician visits and hospitalisations and would also be associated with quality of life benefits as patients would be able to achieve more.

2 Dronedarone (Multaq) for atrial fibrillation

Application

2.1 The Subcommittee reviewed a memorandum from PHARMAC staff regarding the place in therapy of dronedarone for the treatment of atrial fibrillation or flutter.

Recommendation

2.2 The Subcommittee **recommended** that the dronedarone be listed in the Pharmaceutical Schedule with a medium priority subject to the following Special Authority criteria:

> Initial application – Cardiologist only. Approvals valid for 12 months for patients meeting the following criteria:
> All of the following:
> 1 The patient has non-permanent atrial fibrillation or flutter (the risks of dronedarone in permanent conditions outweigh the benefits);
> 2 Class I and Class III antiarrhythmic drugs have been considered (ie flecainide, sotalol, amiodarone, disopyramide and propafenone);
> 3 Digoxin dose adjustment will occur (if relevant);

4 The patient does not have heart failure or left ventricular systolic dysfunction with an ejection fraction < 40% (the risks of dronedarone in these conditions outweigh the benefits);
5 The patient has not experienced previous liver or lung injury*

* liver and lung function monitoring is recommended

Renewal application – Cardiologist only. Approvals valid for 12 months for patients meeting the following criteria:

All of the following:

1 The patient continues to have non-permanent atrial fibrillation or flutter; (the risks of dronedarone in permanent conditions outweigh the benefits)
2 The patient has not developed heart failure or is at high risk of developing heart failure; (the risks of dronedarone outweigh the benefits)

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (iv) The clinical benefits and risks of pharmaceuticals;*

Discussion

2.3 The Subcommittee noted that in September 2011 it had reviewed dronedarone for the treatment of non-permanent and permanent atrial fibrillation (AF) and recommended that it should be deferred until its safety and risk/benefit profile is clarified. The Subcommittee noted that this was on the basis of a safety communication from the FDA (January 2011) following several case reports of hepatocellular liver injury and hepatic failure, the discontinuation of the PALLAS trial as the result of a significant increase in cardiovascular events in the dronedarone arm, a review of dronedarone's risk/benefit profile being carried out by the European Medicines Agency (EMA), and an examination of the trial databases by the supplier in an effort to clarify the adverse effects profile.

2.4 The Subcommittee noted that since then the PALLAS trial had been published, that Sanofi had indicated that it had completed its examination of the trial database, and the European Medicines Agency's Committee had made a recommendation.

2.5 The Subcommittee noted that the current anti-arrhythmic medications used for maintaining sinus rhythm in atrial fibrillation/flutter have been shown to be suboptimal due to significant adverse side-effects and even a trend towards increased mortality versus placebo (Freemantle et al. Europace. 2011; 13 (3): 329-345. doi: 10.1093/europace/euq450).

2.6 The Subcommittee noted that when dronedarone was developed, the intention was to obtain the same efficacy as amiodarone, as it is pharmacologically related to amiodarone, but without its adverse effect profile.

2.7 The Subcommittee noted that in the DIONYSOS study (J Cardiovasc Electrophysiol. 2010; 21: 597-605) the efficacy and safety of amiodarone and dronedarone was compared in 504 patients with persistent atrial fibrillation in a double blind randomised control trial with a median duration of 7 months. The Subcommittee noted that the study found that dronedarone was less effective than amiodarone in decreasing recurrence of atrial fibrillation (36.5% recurrence versus 24.3%) but had a better safety profile with respect to thyroid and neurologic events (0.8% versus 5.9% and 1.2% versus 6.7% respectively) and also did not interact with oral anticoagulants.

2.8 The Subcommittee noted that in the EURIDIS and ADONIS trials (N Engl J Med. 2007; 357: 987-999) the efficacy of dronedarone versus placebo in maintaining sinus rhythm in atrial fibrillation or flutter (not permanent) was compared in 828 patients in two double blind randomised control trial over 12 months (a European trial and a non-European trial). The Subcommittee noted that in the combined trials the median time to first recurrence of atrial fibrillation or flutter was 53 days versus 116 days (placebo versus dronedarone), the recurrence rate at 12 months was 75.2% versus 64.1% ($p<0.001$: NNT=11.1) and the hospitalisation or death rate was 30.9% versus 22.8% ($p=0.01$: NNT=8.1). The Subcommittee noted that the rates of pulmonary toxic effects and of thyroid and liver dysfunction were not significantly different.

2.9 The Subcommittee noted that the ATHENA trial (N Engl J Med. 2009; 360: 668-678) evaluated the effect of dronedarone versus placebo on cardiovascular events in a double blind randomised control trial of 4628 patients with paroxysmal or persistent atrial fibrillation or flutter who were over 75 years of age or who were over 70 years of age with an additional risk factor. The Subcommittee noted that after a mean follow-up of 21 months that the primary outcome (first hospitalisation due to cardiovascular events or death) occurred less in the dronedarone group than in the placebo group (31.9% versus 39.4%: $p<0.001$: NNT=13) as did first hospitalisation due to cardiovascular events (29.3% versus 36.9%: $p<0.001$: NNT=13). The Subcommittee also noted that there was no significant difference in death rate from any cause but that there was a reduction in the death rate from cardiovascular causes with dronedarone (2.7% versus 3.9%: $p=0.03$: NNT=83) largely due to a reduction in the rate of death from arrhythmia (1.1% versus 2.1%: $p=0.01$: NNT=100).

2.10 The Subcommittee noted that following the success of the ATHENA trial the supplier investigated whether dronedarone also provided benefit in higher risk permanent atrial fibrillation patients as examined in the PALLAS trial.

2.11 The Subcommittee noted that in the PALLAS randomised double blind controlled trial (N Engl J Med. 2011; 365: 2268-2276) of 3236 patients who were least 65 years of age and had at least a 6-month history of permanent atrial fibrillation with risk factors for major vascular events who received usual care plus dronedarone or usual care plus placebo. The Subcommittee noted that the trial was stopped for safety reasons on the basis of there being a significantly higher number of the following endpoints with dronedarone versus placebo:

(a) Stroke/myocardial infarction/systemic embolism/death from cardiovascular causes (43 versus 19: $P = 0.002$)

(b) Unplanned hospitalisation for cardiovascular causes or death (127 versus 67: $P<0.001$)

(c) Deaths from cardiovascular causes (21 versus 10: $P = 0.046$)

(d) Death from arrhythmia (13 versus 4: $P = 0.03$)

(e) Stroke (23 versus 10: $P = 0.02$)

(f) Hospitalization for heart failure (43 versus 24: $P = 0.02$)

2.12 The Subcommittee also noted that the ANDROMEDA trial (N Engl J Med. 2008; 358: 2678-2687 – Erratum N Engl J Med. 2010; 363: 1384) had also been stopped due to a higher

death rate but that these patients (97%) had moderate to severe congestive heart failure (class II or III).

2.13 The Subcommittee noted an accompanying editorial to the PALLAS trial (N Engl J Med. 2011; 365: 2321-2322) concluded that the reason why dronedarone was harmful in PALLAS yet beneficial in ATHENA was unclear, that patients with permanent atrial fibrillation should not receive dronedarone, that dronedarone should be avoided in high-risk patients with non-permanent atrial fibrillation (particularly those with heart failure), dose adjustment of digoxin is essential, and that dronedarone should be reserved for selected low-risk patients with persistent or paroxysmal atrial fibrillation, possibly those in whom other antiarrhythmic drugs have failed.

(a) The Subcommittee noted that the European Medicines Agency's Committee considered that the availability of a range of treatments for a difficult condition such as atrial fibrillation was important and that for some patients with non-permanent atrial fibrillation dronedarone is a useful option as the benefits in these patients outweigh the risks. The Subcommittee noted that the European Medicines Agency's Committee recommended:

(b) Restricting the use of dronedarone to maintaining heart rhythm in patients with paroxysmal or persistent atrial fibrillation for the maintenance of sinus rhythm after successful cardioversion.

(c) Dronedarone is not used in patients when atrial fibrillation is still present.

(d) Dronedarone should only be prescribed after alternative treatment options have been considered due to an increased risk of liver, lung and cardiovascular events.

(e) Dronedarone should not be used in patients with permanent atrial fibrillation, heart failure or left ventricular systolic dysfunction (impairment of the left side of the heart).

(f) Dronedarone should be discontinued if atrial fibrillation reoccurs.

(g) Dronedarone should not be used in patients with previous liver or lung injury following treatment with amiodarone.

(h) When dronedarone is used patients lung and liver function and heart rhythm should be regularly reviewed with close monitoring during the first few weeks of treatment.

2.14 The Subcommittee concluded that the DIONYSOS, EURIDIS, ADONIS, and ATHENA trials suggested that dronedarone was probably safer than the alternatives and more effective than placebo but less effective than amiodarone in patients with paroxysmal or persistent atrial fibrillation or flutter. However the Subcommittee concluded that in permanent atrial fibrillation and in congestive heart failure the PALLAS and ANDROMEDIA trials indicated that dronedarone did more harm than good.

2.15 The Subcommittee noted that the European Medicines Agency review (22 September 2011) which included consideration of the post-marketing safety issues and the results of the PALLAS trial considered that dronedarone still has a place in therapy but not in permanent atrial fibrillation and while it is appropriate for persistent atrial fibrillation, the patient population was more restricted than what was used in the ATHENA study.

2.16 The Subcommittee considered that currently there are no satisfactory treatment options for some patients. The Subcommittee considered that this included patients with both coronary disease and asthma as flecainide and sotalol are inappropriate, the toxicity profile of amiodarone is a concern, and ablation is not always appropriate.

2.17 Overall the Subcommittee considered that there is a lack of suitable antiarrhythmic drugs, those that are available are not ideal and that there is an existing unmet clinical need. The Subcommittee considered that while there was some concern with dronedarone, there are currently no better alternatives for some patients.

2.18 The Subcommittee recommended the use of dronedarone in highly symptomatic patients with paroxysmal or persistent atrial fibrillation or flutter who do not have heart failure or associated risk factors.

2.19 The Subcommittee recommended that dronedarone should not be used in permanent atrial fibrillation and that if it was commenced in persistent atrial fibrillation and the patient progressed to permanent atrial fibrillation then dronedarone treatment should be stopped.

3 Ticagrelor for Acute Coronary Syndromes

Application

3.1 The Subcommittee reviewed a funding application from Astra Zeneca for the listing of ticagrelor (Brilinta) on the Pharmaceutical Schedule for the treatment of acute coronary syndromes (unstable angina, ST-elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI)) in patients who are medically managed, managed with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

Recommendation

3.2 The Subcommittee **recommended** that ticagrelor is funded with high priority subject to the following Special Authority criteria:

Initial application only from a relevant medical practitioner. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1 Any of the following:
- 1.1 Patient has been diagnosed with ST-elevation myocardial infarction in the last 24 hours; or
- 1.2 All of the following:
  - 1.2.1 Patient has been diagnosed with non ST-elevation acute coronary syndrome in the last 24 hours; and
  - 1.2.2 Patient has ischaemic chest pain of at least 20 minutes unresponsive to nitroglycerin; and
  - 1.2.3 Patient has an elevated troponin level (high sensitivity troponin T >50ng/L or troponin I above the reference range) with a documented rise and/or fall; and
  - 1.2.4 At least one of the following: age >60 years, previous coronary event, previous cerebrovascular event, diabetes mellitus, peripheral arterial disease, chronic renal dysfunction and/or dynamic ST elevation or depression >1mm on electrocardiogram; and

2 Patient has not received fibrinolytic therapy in the last 24 hours or fibrinolysis is not planned; and

3 Any of the following:
3.1 Patient has not received a loading dose of clopidogrel in the last 3 days or
3.2 Patient is clopidogrel-allergic*

*Clopidogrel allergy is defined as a history of anaphylaxis, urticaria, generalised rash or asthma (in non-asthmatic patients) developing soon after clopidogrel is started and is considered unlikely to be caused by any other treatment.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

3.3 The Subcommittee noted that PTAC had reviewed the funding application for ticagrelor at its November 2011 but had deferred making a recommendation and instead had referred the application to the Cardiovascular Subcommittee for its view on the ticagrelor's place in therapy including:

(a) an indication of the quality of the evidence and the Subcommittee's confidence as to whether the absolute risk reduction achieved in the PLATO trial would be achieved in clinical practice;

(b) the Subcommittee's view as to the extent of the outcomes of the PLATO trial being achieved in clinical practice; and

(c) the identification of patient groups and lengths of treatment which would result in the greatest clinical benefit being obtained with ticagrelor for the purposes of targeting therapy to those with the highest clinical need and for periods where it would provide the greatest health benefit.

3.4 The Subcommittee also noted that the supplier had provided a response to some of the issues raised by PTAC at its November 2011 meeting.

3.5 The Subcommittee noted the results of from the CURE (Mehta et al. Eur Heart J 2000; 21: 2033-2041), PCI-CURE (Mehta et al. The Lancet 2001; 358 (9281): 527-533) and TRITON (Wiviott SD, et al. N Engl J Med. 2007;357:2001-15) trials for the use of clopidogrel and prasugrel in patients with acute coronary syndromes (ACS).

3.6 The Subcommittee noted that prasugrel when compared to clopidogrel in the TRITON trial showed an absolute risk reduction (ARR) of 2.2% (p <0.001, HR 0.81, 95%CI 0.73-0.90) for the primary endpoint of cardiovascular (CV) death, myocardial infarction (MI) and cerebrovascular accident (CVA). The Subcommittee noted that when comparing mortality rates between prasugrel and clopidogrel in that trial, there was no significant difference (mortality CV causes – prasugrel 2.1% versus clopidogrel 2.4% (p=0.31) and mortality any cause – prasugrel 3.0% versus clopidogrel 3.2% (p=0.64)).

3.7 The Subcommittee noted that in the PLATO trial (Wallentin L et al. N Engl J Med; 361: 1045-57), the use of ticagrelor when compared to clopidogrel resulted in an ARR of 1.9% (p<0.001, HR 0.84, 95% CI 0.77 to 0.92) for the primary endpoint of death from vascular causes, MI and CVA. The Subcommittee noted also that unlike prasugrel, ticagrelor was associated with a significantly lower mortality rate when compared to clopidogrel (mortality

vascular causes – ticagrelor 4.0% versus clopidogrel 5.1% (p=0.001) and mortality any cause – ticagrelor 4.5% versus clopidogrel 5.9% (p<0.001)). The Subcommittee also noted that the additional benefit of ticagrelor for mortality shown in the PLATO trial was not associated with an increased risk of bleeding when compared to clopidogrel except for fatal intracranial bleeding (ticagrelor 0.1% versus clopidogrel 0.01%, p=0.02).

3.8 The Subcommittee considered that the patients included in the PLATO trial had a higher risk of having a further cardiovascular event i.e they were a more unwell population, than those patients included in the TRITON trial as 38% of patients included in the PLATO trial had ST-elevation myocardial infarctions (STEMI) compared to 25% in the TRITON trial.

3.9 The Subcommittee considered it was difficult to compare prasugrel to ticagrelor without a head-to-head trial and that while such a trial was desirable it was unlikely to be performed.

3.10 The Subcommittee also noted that the stent thrombosis (probable or definite) rates for prasugrel (HR 0.48, 95% CI 0.36-0.64, p<0.001) were lower when compared to clopidogrel than with ticagrelor (HR 0.75, 95%CI 0.59-0.95, p=0.02) versus clopidogrel. The Subcommittee considered that prasugrel may therefore be preferred over ticagrelor for patients in whom the increased risk of stent thrombosis outweighs the increased risk of bleeding with prasugrel.

3.11 The Subcommittee considered that the absolute risk reduction likely to be achieved with ticagrelor in New Zealand patients would be lower than that observed in the PLATO trial but still higher than what would be likely with the use of prasugrel.

3.12 The Subcommittee considered that there is no clear explanation for why the Kaplan-Meier curves (cumulative incidence of primary endpoint) for ticagrelor continue to diverge up to 12 months unlike the previous trials for clopidogrel or prasugrel. The Subcommittee considered that it was possible that ticagrelor prevented more early events which would reduce the long term risk and this effect could be more pronounced in a higher risk population as was investigated in the PLATO trial..

3.13 The Subcommittee noted the results from the North American cohort in the PLATO trial where clopidogrel was observed to be more efficacious than ticagrelor for the primary endpoint (ticagrelor 11.9% versus clopidogrel 9.6%, HR 1.25, 95%CI 0.93 -1.67). The Subcommittee considered that the different aspirin dosing or chance could potentially explain the results. The Subcommittee considered that it was reassuring that ticagrelor was found to be more efficacious than clopidogrel for the primary endpoint in the Asia Pacific cohort (ticagrelor 9.8% versus clopidogrel 11.7%, HR 0.84, 95%CI 0.77 – 0.92). The Subcommittee noted the funnel plot of log hazard ratio by events per country generated by the FDA statistical review (Fiorentino. Clinical Efficacy Review, NDA 022433 Birlinta, ticagrelor. FDA, June 2010. Clinical efficacy review, page 65. Figure 24. Funnel plot by Country. Available at http;//www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220192.pdf) and considered that Poland and Hungary were not significant outliers.

3.14 The Subcommittee considered the possibility of reduced patient compliance with ticagrelor (twice daily treatment) when compared to clopidogrel (once daily treatment) could not be accurately compared in the PLATO trial because all patients were on a twice daily treatment regime to maintain blinding. The Subcommittee also noted that only 19.6% of patients in the clopidogrel arm received the higher appropriate loading dose of 600mg and that both of these factors could bias the trial results in favor of ticagrelor. The Subcommittee also noted

that breathlessness was a significant side effect from ticagrelor and would result in some patients discontinuing treatment.

3.15 The Subcommittee noted that PTAC had requested the Cardiovascular Subcommittee's advice on identifying lengths of treatment which would result in the greatest clinical benefit being obtained with ticagrelor for the purposes of targeting therapy for periods where it would provide the greatest health benefit. The Subcommittee noted that the greatest benefit was obtained in the first six months with additional benefit, although smaller continuing to be gained up until 12 months. The Subcommittee considered that it would be inappropriate to try to elicit the possibility of shorter treatment durations from the PLATO study results because it was not designed to investigate different durations of treatment prospectively.

3.16 The Subcommittee noted the preliminary results from the PRODIGY trial presented at the 2011 European Society of Cardiology conference showed that 6 months treatment is not inferior to 24 months treatment with dual antiplatelet therapy following cardiac stenting. The Subcommittee noted that 6 months treatment with ticagrelor was more cost-effective than 12 months treatment but considered that there is currently insufficient evidence from the PLATO trial to support that shorter duration of treatment.

3.17 The Subcommittee noted that PTAC had reviewed the evidence in regards to platelet function and genetic testing and its utility in targeting antiplatelet therapy at its November 2011 meeting. The Subcommittee considered that there is evidence to support that patients with some genetic polymorphisms do poorly on clopidogrel, that this could be the case for Maori and Pacific peoples and could provide a rationale for providing prasugrel or ticagrelor to those patient groups. However, the Subcommittee agreed with PTAC's recommendation that there is currently insufficient evidence for the use of these tests in clinical practice and it would be difficult to implement them due to multiple logistical issues including the timing and interpretation of test results.

3.18 The Subcommittee considered that the efficacy of ticagrelor was consistent across all subgroups of patients with acute coronary syndromes (ACS) including those undergoing PCI/CABG or medical management. The Subcommittee considered that it would be appropriate to assume for the purpose of the cost-utility analysis that a patient would be at normal population risk of events after one year of treatment.

3.19 The Subcommittee considered that it would be appropriate to model the ticagrelor Special Authority based on the PLATO inclusion and exclusion criteria. Based on this, the Subcommittee considered that if this is done, a third of new clopidogrel/prasugrel patients would use ticagrelor in preference to prasugrel or clopidogrel on the basis of the mortality benefit.

3.20 The Subcommittee noted that enrolment into the PLATO trial was prior to the introduction of high sensitivity Troponin T and I assays which is now widely used in New Zealand. The Subcommittee considered that these high sensitivity assays would result in more false positives and clinicians should not rely on single measurements of these biomarkers alone to diagnose ACS.

3.21 The Subcommittee considered that if there was a need to further tighten the Special Authority criteria to increase the cost-effectiveness or reduce the budget impact of funding ticagrelor, the criteria could be amended to exclude patients with unstable angina and require the high sensitivity troponin levels to be twice that of the reference range which would be more analogous to the troponin assays used in the PLATO trial.

The Subcommittee noted that those patients with STEMIs who received fibrinolytic therapy within the last 24 hours were excluded from the PLATO trial. The Subcommittee considered that this should be an exclusion criterion on the Special Authority as there is currently no data on the safety or efficacy of ticagrelor in combination with fibrinolysis. The Subcommittee also considered that it would not be appropriate to switch patients who received a clopidogrel loading dose to ticagrelor.

4 Ivabradine for inappropriate sinus tachycardia

Application

4.1 The Subcommittee reviewed a memorandum from PHARMAC staff regarding the listing of ivabradine on the Pharmaceutical Schedule for the treatment of inappropriate sinus tachycardia (IST).

Recommendation

4.2 The Subcommittee **recommended** that ivabradine be listed in the Pharmaceutical Schedule with a high priority for patients with inappropriate sinus tachycardia subject to the following Special Authority criteria:

SAXXXX Special Authority for Subsidy
Initial application (Inappropriate Sinus Tachycardia) – Cardiologist only. Approvals valid for 12 months for patients meeting the following criteria:
All of the following:

1. The patient has been diagnosed with Inappropriate Sinus Tachycardia in accordance with the following criteria;
    i. The patient has a Holter ECG assessed mean daytime heart rate of over 100 beats per minute or a mean 24 hour heart rate of over 90 beats per minute; and
    ii. Other arrhythmias have been excluded; and
    iii. Endocrine disorders have been excluded; and
2. The patient continues to have inappropriate sinus tachycardia and has failed therapy with beta-blockers and calcium channel blockers (unless not tolerated or contraindicated).

Renewal application – (Inappropriate Sinus Tachycardia) - Cardiologist only. Approvals valid for 12 months for patients meeting the following criteria:
All of the following:

1. The patient has been assessed for spontaneous recovery from Inappropriate Sinus Tachycardia through a 2 week ivabradine drug holiday;

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (iv) The clinical benefits and risks of pharmaceuticals.*

Discussion

4.3 The Subcommittee noted that IST is an uncommon condition characterised by an elevated resting heart rate (defined as over 100 beats/minute when awake and a 24 hour average over 90 beats/minute) and an exaggerated heart rate response to minimal physical activity.

4.4 The Subcommittee noted that IST predominantly affects young women and considered that perhaps there would be 20 to 50 patients in New Zealand.

4.5 The Subcommittee noted that diagnosis was difficult with exclusion of other conditions being required and that IST has few treatment options. The Subcommittee noted that first-line treatments included the use of beta-blockers and calcium channel blockers. The Subcommittee noted that ablation can be used but considered this to be the last-line treatment as its success is variable and it has a high recurrence rate within two years.

4.6 The Subcommittee noted that ivabradine decreases the depolarizing I_f current in the sinoatrial node which results in a reduced heart rate.

4.7 The Subcommittee noted that while ivabradine is not registered in New Zealand it is registered internationally for angina and heart failure. The Subcommittee also noted that while ivabradine is not registered for IST its mechanism of action and its ability to reduce heart rate means that it is a treatment option for IST.

4.8 The Subcommittee noted that there are a small number of patients with IST currently being treated with ivabradine in New Zealand (perhaps 6 to 10) through a compassionate supply program run by Servier out of Australia.

4.9 The Subcommittee noted that the evidence for ivabradine in IST is limited to two cohort studies containing 13 and 18 patients respectively and a number of case studies.

4.10 The Subcommittee noted a study by Rakovec (Wiener klinische Wochenschrift (The Middle European Journal of Medicine) 2009; 121:715-718) which found that 15 mg of ivabradine per day reduced the mean daily heart rate in 12 patients with IST from 94.0 to 74.6 bpm ($p<0.005$) and decreased the highest heart rate in 10 of the patients (those who could be reliably measured) from 150.3 to 120.6 bpm and the lowest heart rate from 66.7 to 54.8 bpm (both $p<0.005$).

4.11 The Subcommittee noted a study by Calo et al (Heart Rhythm 2010; 7:1318–1323) which found that ivabradine (average dose 5 mg twice daily) significantly reduced the mean heart rate in 18 patients with symptomatic IST as assessed by 24 hour Holter from 98 bpm (baseline) to 76 bpm (at 3 months) and to 68 bpm (at 6 months) and decreased the maximal heart rate from 151 to 124 and 111 bpm for the same periods with the minimal heart rate slightly decreasing at 3 months and then stabilising. The Subcommittee noted that in 12 of the patients a complete disappearance of symptoms was observed at 3 months and that this occurred in all of the patients at 6 months. The Committee noted that in exercise testing the heart rate decreased and the maximal load also increased.

4.12 The Subcommittee noted that the safety and efficacy of ivabradine for lowering heart rate was shown in the large randomized BEAUTIFUL Holter Substudy of ivabradine versus placebo (Tendera et al. Am J Cardiol 2011; 107:805) although it noted that these patients did not have IST.

4.13 The Subcommittee noted that overall the evidence was not strong but that it was unlikely to get any better.

4.14 The Subcommittee considered that IST was a debilitating disease and that while ivabradine would not improve mortality, it would improve a patient`s quality of life including reducing/eliminating tachycardia and the fear of it (which the Subcommittee considered has a significant debilitating effect) and enabling a return to work.

4.15 The Subcommittee considered that ivabradine should be funded for IST (defined by a Holter ECG assessed daytime heart rate of over 100 beats/minute and mean 24 hour heart rate of over 90 beats/minute, with other causes of palpitation and chronic fatigue being excluded) following treatment with beta-blockers and calcium channel blockers (but not digoxin due to efficacy and toxicity issues) for IST with a high priority. The Subcommittee considered ivabradine to be preferable to ablation as this is an expensive option with high relapse rates and is not without complications.

4.16 The Subcommittee considered that some patients may spontaneously recover and therefore a 12 monthly renewal following a 1-2 week drug holiday would be appropriate.

4.17 The Subcommittee also considered that a short course of ivabradine may be appropriate for use in asthmatics undergoing cardiac CT/MRI as it would slow their heart rate and improve image quality where beta blockers are contra-indicated.