Cardiovascular Subcommittee of PTAC meeting held 7 October 2010

(minutes for web publishing)

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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 17 & 18 February 2011, the record of which is available on the PHARMAC website.

Contents

1 Relevant PTAC minutes

1.1 The Subcommittee noted the following PTAC minutes:

1.1.1 November 2008 - Tredaptive (extended release nicotinic acid with laropripant) – The Subcommittee agreed with PTAC's recommendation to decline the application on the basis of a lack of long-term efficacy and safety data.

1.1.2 February 2009 – Rosuvastatin - The Subcommittee agreed with PTAC's recommendation for rosuvastatin to be listed with medium priority as a third-line cholesterol lowering agent after treatment failure with simvastatin and atorvastatin. The Subcommittee considered that pravastatin was a possible alternative if patients were purely intolerant to simvastatin and atorvastatin, with rosuvastatin potentially being useful in patients who were not reaching their low density lipoprotein (LDL) targets with the maximal tolerated dose of atorvastatin. It noted that the STELLAR study (Jones et al. Am J Cardio. 2003 Jul 15; 92(2):152-60) showed that atorvastatin 80 mg and rosuvastatin 20 mg and 40 mg have the same or similar therapeutic effect. The Subcommittee considered that rosuvastatin could be limited by a short Special Authority approval period of 3 months for initial applications to ensure that the patient is reviewed and is truly benefitting from treatment. The Subcommittee noted that ezetimibe was another alternative for third-line treatment but statins should be trialled first. Given the present uncertainties over ezetimibe's clinical outcomes, other options (rosuvastatin and/or pravastatin) would be useful.

1.1.3 February 2010 – Fenofibrate - The Subcommittee agreed with PTAC's decline recommendation and noted that both bezafibrate and gemfibrozil will be available from 1 December 2010.

1.1.4 August 2010 – Bisoprolol – The Subcommittee agreed with PTAC's recommendation that bisoprolol be listed on the Pharmaceutical Schedule with medium priority for the treatment of chronic heart failure.

2 Phenindione

2.1 The Subcommittee noted that there have been a number of requests for phenindione through Hospital and Community Exceptional Circumstances (HEC and CEC) for patients with warfarin allergy. The Subcommittee noted that phenindione is not listed in Section B of the Pharmaceutical Schedule but is available through Discretionary Community Supply (DCS) for patients with warfarin resistance. The Subcommittee **recommended** that access to phenindione on DCS is widened to include patients with warfarin intolerance. The Subcommittee considered that the definition of warfarin intolerance was more appropriate than warfarin allergy for this patient group.

3 Enoxaparin

3.1 The Subcommittee noted the difficulties with enoxaparin dispensing currently as community pharmacies are hesitant to stock it given the risk of unused stock and the difficulty around manual Special Authority applications after hours and over the weekends. The Subcommittee noted that there are no issues when the Special Authority is applied for electronically and enoxaparin can be obtained from hospital pharmacies. The Subcommittee considered that some of these problems can be addressed by accident and medical clinics having designated community pharmacies which stock enoxaparin.

3.2 The Subcommittee noted that the EC Panel has asked PHARMAC to consider widening access to enoxaparin in Section B of the Pharmaceutical Schedule for patients with Protein C and/or S deficiencies who have experienced thromboembolic events whilst on warfarin therapy. The Subcommittee **recommended** that access is widened to include this patient group with a medium priority.

4 Lipid modifying agents

4.1 The Subcommittee noted that PHARMAC has received requests from clinicians to list a long-acting nicotinic preparation. The Subcommittee **recommended** that PHARMAC list a long acting preparation of nicotinic acid with medium priority if it could source one as it would reduce flushing. The Subcommittee agreed with the Tender Medical Subcommittee's view that the 375mg and 500mg strengths of long-acting nicotinic acid were essential but that a range would be useful.

4.2 The Subcommittee noted that PHARMAC has received requests to widen access to pravastatin and there have been applications for it through Community Exceptional Circumstances (CEC). The Subcommittee **recommended** that PHARMAC widen access to pravastatin for patients who are intolerant to the currently listed statins. The Subcommittee noted that unlike simvastatin and atorvastatin, pravastatin is not metabolised by the CYP 3A4 metabolic pathway and that while it is not very potent there is good outcome data to support its use. The Subcommittee considered that open listing would not be a significant fiscal risk as it would not be used as a first or second line therapy.

4.3 The Subcommittee noted that PHARMAC had received a request from a clinician to list omega-3 polyunsaturated fatty acid on the basis that it reduces LDL cholesterol. The Subcommittee noted that LDL cholesterol is a surrogate marker and that there is currently a lack of outcome evidence that it results in reduced morbidity or mortality. The Subcommittee **recommended** that omega-3 polyunsaturated fatty acid is not listed on the Pharmaceutical Schedule, although this could be reviewed if new outcome evidence becomes available.

4.4 The Subcommittee noted that PHARMAC has received requests from clinicians to consider listing coenzyme Q10 for use in conjunction with statins in patients intolerant of statins when used on its own. The Subcommittee considered that there is currently an absence of evidence to support its use but noted that a clinical trial is underway which is investigating the efficacy of coenzyme Q10 in statin intolerance. The Subcommittee **recommended** that coenzyme Q10 is reviewed if supporting evidence becomes available.

5 Prasugrel for patients undergoing percutaneous coronary intervention (PCI)

5.1 The Subcommittee reviewed a re-submission from Eli Lilly for prasugrel (Effient) after PTAC previously recommended its application for funding be declined in February 2010. The Subcommittee noted that after reviewing this re-submission from Eli Lilly in August 2010, PTAC deferred making a recommendation until it was reviewed by the Subcommittee.

5.2 The Subcommittee considered that although prasugrel and clopidogrel were both thienopyridines, prasugrel was more potent. Prasugrel also had a more rapid onset of action where 50% inhibition of platelet inhibition was achieved in 30 minutes as opposed to 2 hours with clopidogrel (Payne CD. Transcatheter Cardiovascular Therapeutics; Washington DC 2006.Abstract 16). The interpatient variability for inhibition of platelet aggregation for prasugrel was also less compared to clopidogrel (Brandt JT et al. Am Heart J. 2007; 153: 66.e9-e16).

5.3 The Subcommittee noted that the application for the listing of prasugrel was based on the TRITON TIMI-38 trial (Wiviott SD, et al. N Engl J Med. 2007; 357: 2001-2015). The trial involved 13,608 patients and was adequately randomised. Treatment was started at the time of decision to perform PCI (prasugrel loading dose of 60mg then 10mg/day versus clopidogrel loading dose of 300mg then 75mg/day). The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke. The key safety endpoint was major bleeding.

5.4 The Subcommittee considered that although the primary endpoint was reached in significantly less patients in the prasugrel group (9.9% versus 12.1%; HR 0.81; 95% CI 0.73 to 0.90; $p<0.001$), the result was predominantly driven by the reduction in nonfatal MIs by prasugrel. The Subcommittee considered that the use of a composite endpoint as the primary endpoint was a weakness of the trial. The composite endpoint did not include outcomes of equivalent impact or of similar rate. The Subcommittee also considered that the significance of the non-fatal MI endpoint was uncertain as it included post-procedure and asymptomatic biomarker rise. However, the Subcommittee noted that when the data was re-analysed using the Universal Definition of MI, the result was still significantly in favor of prasugrel.

5.5 The Subcommittee considered that the loading dose and timing of treatment in the clopidogrel treatment arm were not representative of the current standard of care and could have biased the results in favour of prasugrel. Currently, patients are pre-loaded

with 600mg of clopidogrel whereas in the trial, 74% of patients were loaded with 300mg clopidogrel mid-procedure.

5.6 The Subcommittee noted the results of the CURRENT-OASIS 7 trial which was recently published as two separate papers; one reporting the overall results (The CURRENT-OASIS 7 Investigators. N Engl J Med 2010; 363: 930-42) and another for the subgroup that underwent PCI (Mehta SR, et al. Lancet 2010). The trial investigated the efficacy of double-dose clopidogrel (600mg loading dose, followed by 150mg/day for 6 days then 75mg/day thereafter) versus standard-dose clopidogrel (300mg loading dose, 75mg/day thereafter) for patients with acute coronary syndromes and those undergoing PCI. The primary outcome for was a composite of cardiovascular death, MI and stroke at 30 days. There was no significant difference between the two treatment arms with respect to the primary outcome in patients with acute coronary syndrome who were referred for an invasive strategy (4.2% versus 4.4% for double-dose and standard-dose respectively; HR 0.94; 95% CI 0.83-1.06; p=0.30). However, in the patients who ended up undergoing PCI, the primary outcome for double-dose clopidogrel was significantly lower (3.9% versus 4.5%; HR 0.86; 95% CI 0.74-0.99; p=0.039). There was however no significant difference in the primary outcome when the diabetic and STEMI subgroups were analysed.

5.7 The Subcommittee also noted that data from the Food and Drug Administration (FDA) had revealed that prasugrel may be associated with an increased incidence of cancer although this remains to be confirmed and is being further investigated in the TRILOGY ACS trial.

5.8 The Subcommittee noted that the TRITON TIMI-38 trial showed that there was an increased bleeding risk with prasugrel which continued throughout the treatment period. Subgroups at increased risk included patients >75 years old, weight <60kg, patients with renal impairment, patients with other bleeding risk (including thrombolysis) and patients who underwent coronary arterial bypass graft (CABG) surgery. The Subcommittee considered that the increased bleeding risk with prasugrel may be reduced with the increased use of the radial route in current practice as compared to the femoral route in the TRITON TIMI-38 trial. The Subcommittee also noted that subgroups at increased bleeding risk also had a 2% increase in thrombotic events in the prasugrel cohort.

5.9 The Subcommittee noted that in the subgroup analysis (Wiviott SD, et al. Circulation 2008) for diabetics included in the TRITON TIMI-38 trial, there was a larger absolute risk reduction (ARR) of 4.8% (HR 0.70; p<0.001) for the composite primary endpoint in patients treated with prasugrel. However, the Subcommittee considered that this evidence was weak and there is very little difference between prasugrel in diabetics and non-diabetics as the interaction term for the result was not significant (p=0.09).

5.10 The Subcommittee noted the subgroup analysis for the STEMI subpopulation (Montalescot G, et al. Lancet 2009; 373: 723-731), prasugrel was associated with a 2.4% ARR (HR 0.79; p=0.022)) in the primary endpoint over 15 months. The Subcommittee noted in this patient group prasugrel offered the most benefit in patients who would undergo an immediate catheterisation procedure immediately due to its potentially faster onset of action than clopidogrel. The Subcommittee also noted that NSTEMI patients would have time for a clopidogrel loading dose.

5.11 The Subcommittee noted that the primary endpoint results from the TRITON TIMI-38 trial for prasugrel were not affected by polymorphisms of the CYP2C19 gene in patients unlike clopidogrel (Mega JL, et al. Circulation 2009; 119: 2553-2560). However, the Subcommittee considered that there were many challenges in the practicalities of genetic testing currently and there is still uncertainty around the significance of the CYP2C19 genetic polymorphisms (Parẽ G, et al. N Engl J Med 2010). The Subcommittee considered that further evidence is needed before conclusions on the significance of these genetic polymorphisms can be made.

5.12 The Subcommittee noted that for the pre-specified secondary endpoint of stent thrombosis in the TRITON TIMI-38 trial, prasugrel demonstrated a significant benefit across a broad range of patient subpopulations (Wiviott SD, et al. Lancet 2008; 371 (9621): 1353–1363). With the exception of patients ≥75 years of age, the reductions were statistically significant, however, the absolute numbers were small.

5.13 The Subcommittee considered that although patients received 15 months treatment with prasugrel in the TRITON TIMI-38 trial, the most benefit when compared to clopidogrel occurred within the first 30 days. Given this and its high cost the Subcommittee considered that it was appropriate to limit prasugrel to shorter treatment durations. The Subcommittee noted that by 3 months the endothelium covers bare metal stents (BMS) and has covered drug-eluting stents (DES) in 50% of patients. Therefore, while it considered that one month treatment would be acceptable, the Subcommittee considered that 3 months would be more appropriate.

5.14 The Subcommittee noted that prasugrel was currently significantly more expensive than clopidogrel. Due to the high cost of treatment, the Subcommittee considered that prasugrel could be limited by Special Authority to the following patients aged < 75 with a body weight ≥60kg with no prior history of stroke or transient ischaemic attack:

- patients who experienced stent thrombosis whilst on clopidogrel (lifetime access) – on the basis that there is 50% mortality associated with stent thrombosis.

- patients allergic to clopidogrel undergoing PCI (3 months post-angioplasty, 6 months for BMS, 12 months for DES) – on the basis of the durations previously applied to clopidogrel and in-line with current clinical guideline recommendations and that while ticlopidine has previously been used in patients with clopidogrel allergy undergoing PCI there is no trial evidence to support the use of ticlopidine in drug-eluting stents (DES). Clopidogrel allergy is defined as a history of anaphylaxis, urticaria or asthma within 4 hours of ingestion of clopidogrel.

- patients with STEMIs undergoing immediate PCI (3 months) – on the basis that prasugrel has a faster onset of action and therefore would be preferred in patients undergoing immediate catheterisation and patients could be switched to clopidogrel after the 3 months.

5.15 The Subcommittee **recommended** that prasugrel be listed with high priority on the Pharmaceutical Schedule for patients who experienced stent thrombosis whilst on clopidogrel and patients allergic to clopidogrel undergoing PCI. The Subcommittee **recommended that** prasugrel be listed with medium priority for patients with STEMIs

undergoing immediate PCI. The Subcommittee further **recommended** that prasugrel be declined for patients undergoing PCI with diabetes or who have confirmed reduced function allele of the CYP2C19 enzyme on the basis of a lack of evidence.

5.16 The Decision Criteria particularly relevant to this recommendation are: *(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 (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

6 Dabigatran for atrial fibrillation

6.1 The Subcommittee reviewed an application from Boehringer Ingelheim for the listing of dabigatran etexilate (Pradaxa) on the Pharmaceutical Schedule for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation (AF). The Subcommittee noted that dabigatran is currently registered in New Zealand for venous thromboembolism (VTE) prophylaxis post-orthopaedic surgery and registration for the use in AF is expected by the end of 2010.

6.2 The Subcommittee noted that the pivotal trial in the application was the RELY trial (Connolly SJ, et al. N Engl J Med 2009; 361: 1139-51) which was a large multi-centre, multi-national, randomised non-inferiority trial comparing open label warfarin and two doses of dabigatran (220 or 300mg/day in 2 divided doses) in 18,113 patients with AF. The median duration of follow-up was 2 years and the primary outcome was stroke or systemic embolism. The Subcommittee considered that the trial showed that both doses of dabigatran were non-inferior to warfarin for the primary outcome with little difference in major bleeding. The Subcommittee noted that although the trial was a non-inferiority trial, the 300mg dabigatran dose was superior to warfarin for the primary outcome with an ARR of 0.58% (relative risk 0.66; NNT 172; 95% CI 0.53-0.82; $p<0.001$). The Subcommittee noted that there was no difference in hepatic adverse events between any of the three treatment arms but dabigatran was associated with a higher rate of dyspepsia. The Subcommittee considered that this trial was of good quality and grade 1+ level on the SIGN (Scottish Intercollegiate Guidelines Network) rating scheme.

6.3 The Subcommittee noted that there were no comparative studies between dabigatran and aspirin currently available. The Subcommittee noted that a meta-analysis (Hart RG, et al. Ann Intern Med 1999; 134: 492-501) showed that warfarin reduced the absolute risk of stroke by 0.7% compared to aspirin. However, the Subcommittee considered that the results of the BAFTA trial (Mant J, et al. Lancet 2007; 370: 493-503) involving 973 patients which showed an ARR of 2% for warfarin versus aspirin, was more accurate as it was a head-to-head trial directly comparing warfarin and aspirin. From the RELY and BAFTA trials, the Subcommittee considered that dabigatran would probably result in an ARR of 2% for stroke when compared to aspirin. When compared to aspirin, dabigatran would likely be associated with an increased risk of bleeding with an absolute risk increase of 0.9% per year based on the difference in the warfarin arm and aspirin only arm in the ACTIVE-W and ACTIVE-A trials.

6.4 The Subcommittee noted the ACTIVE-W trial (The Active Writing Group. Lancet 2006; 367:1903-12) which was a large multicentre parallel groups study of clopidogrel plus

aspirin versus oral anticoagulation for AF. The primary outcome was the first occurrence of stroke, systemic embolism, myocardial infarction or vascular death. The Subcommittee noted that the median follow up was 1.28 years and the study was discontinued because interim analysis showed superiority of anti-coagulation. The Subcommittee considered that the conclusions from this trial are that the combination of clopidogrel plus aspirin is inferior to oral anticoagulation and possibly results in increased bleeding. The Subcommittee also considered the ACTIVE-A trial (The Active Investigators. N Engl J Med 2009; 360: 2066-78) which was a large multicentre parallel groups study of clopidogrel plus aspirin versus aspirin alone. The primary outcome variable was time to first stroke, myocardial infarction, vascular death or non-CNS metabolism with a median follow up of 3.6 years. The Subcommittee considered that combination clopidogrel and aspirin was superior to aspirin alone with an ARR or 0.8% (NNT 125; 95% CI 0.81-0.98; p=0.01) but with an increased risk or major bleeding (absolute risk increase 0.7%; NNH 142; 95% CI 1.29-1.92; p<0.001). Based on both ACTIVE trials, the Subcommittee considered that clopidogrel in combination with aspirin was inferior to anticoagulation and although evidence suggests it is better than aspirin alone, it is associated with an increased risk of bleeding.

6.5 The Subcommittee concluded that the most appropriate comparators to dabigatran were warfarin and aspirin monotherapies. While the Subcommittee also considered that there would be a group of patients on neither warfarin nor aspirin it concluded that these patients would be unlikely candidates for dabigatran and this patient group was not included in the clinical trials.

6.6 The Subcommittee considered that there is no publication with robust NZ data to estimate the prevalence of AF or the use of warfarin or aspirin as a treatment. The Subcommittee considered that the NZ Guidelines Group estimate that there are approximately 30,000 to 100,000 New Zealanders living with AF (New Zealand Guidelines Group 2005.*The management of people with atrial fibrillation and flutter; xxxi-xxxii*). The Subcommittee noted the supplier estimate of 65,000 patients based on a general practice database *HealthStat*. The Subcommittee considered that there was a higher prevalence of AF among the older population and Maori. as well as Pacific peoples. The Subcommittee considered that approximately 25-40% of patients with AF are using warfarin and most of the remaining patients are using aspirin (30-60%) based on several trials (Burgess C, et al. Ther Clin Risk Manag. 2007 Jun; 3(3): 491-8 and Somerfield J, et al. Stroke 2006; 37: 1217-20). The Subcommittee considered that 10-20% of AF patients may not be on any anti-thrombotic therapy. The Subcommittee considered that it is likely that <1% of AF patients are using dipyridamole or clopidogrel with or without aspirin and likely only in special circumstances.

6.7 The Subcommittee noted the suppliers proposed Special Authority criteria to limit dabigatran to patients with a $CHADS_2$ score of ≥2 and who have trialled warfarin but INR levels failed to be maintained within the therapeutic range or who are contraindicated to warfarin therapy. The Subcommittee considered that the New Zealand Guidelines Group risk assessment tool based on the Framingham study was more commonly used here. Although it was appropriate to limit patients through risk stratification, the Subcommittee considered that it would be very difficult to restrict its use via Special Authority without a significant risk of slippage.

6.8 The Subcommittee noted that while most guidelines do not recommend warfarin for those at very low risk of stroke, the majority of people with AF fall within the intermediate or high risk category and would be candidates for dabigatran. The Subcommittee considered that it is very likely that all patients using warfarin would switch to dabigatran except those with severe renal impairment (GFR <30ml/min) and those allergic or intolerant of it. The Subcommittee also considered that dabigatran would replace aspirin in patients who are taking aspirin because they have a higher risk of an adverse event with warfarin i.e. those intolerant or allergic to warfarin, those with dementia, the very elderly and those on multiple medications. The Subcommittee considered that approximately 30-60% of AF patients currently on aspirin would switch to dabigatran.

6.9 The Subcommittee considered that dabigatran would remove the need for regular venepunctures and the difficulty with drug as well as food interactions with warfarin. The Subcommittee considered that the ease of use of dabigatran would increase the use of anticoagulation and probably reduce the burden of stroke to the health system in those poorly controlled on warfarin or on aspirin. However, the Subcommittee noted that there are risks with dabigatran therapy including a lack of long term outcome and adverse effect data, and no antidote for bleeding from dabigatran, unlike Vitamin K for warfarin. The Subcommittee considered that there would need to be some guidance provided to clinicians to mitigate and manage the bleeding risk if dabigatran is listed.

6.10 The Subcommittee considered that while dabigatran and warfarin were clinically equivalent dabigatran would make management of patients easier and would be an advantage for patients contraindicated or difficult to control with warfarin and are therefore on aspirin. The Subcommittee however noted that it had a much higher cost.

6.11 The Subcommittee **recommended** that dabigatran be listed on the Pharmaceutical Schedule with a medium priority. The Subcommittee considered that listing both strengths of dabigatran would be appropriate to allow for dose-adjustment in certain patient groups including those with renal impairment.

6.12 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (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*