Hospital Pharmaceuticals Review

PTAC, Hospital Pharmaceuticals Subcommittee & Cardiovascular Subcommittee minutes for web publishing

Cardiovascular System therapeutic group

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This document contains minutes relevant to the consultation document of 3 August 2012 relating to products in the Cardiovascular System therapeutic group.

Note that this document is not a complete record of the relevant PTAC and Subcommittee meetings; only the relevant portions of the minutes relating PTAC and its Subcommittees advice on the review of Hospital Pharmaceuticals are included.

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Hospital Pharmaceuticals Subcommittee – 5 April 2011

1 Agents Affecting the Renin-Angiotensin System

1.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Agents Affecting the Renin-Angiotensin System heading.

1.2 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

- Captopril
  - Oral liq 5 mg per ml
  - Tab 12.5 mg
  - Tab 25 mg
  - Tab 50 mg
- Cilazapril
  - Tab 0.5 mg
  - Tab 2.5mg
  - Tab 5 mg
- Enalapril maleate
  - Tab 5 mg
  - Tab 10 mg
  - Tab 20 mg
- Lisinopril dihydrate
  - Tab 5 mg
  - Tab 10 mg
  - Tab 20 mg
- Quinapril
  - Tab 5 mg
  - Tab 10 mg
  - Tab 20 mg
- Cilazapril with hydrochlorothiazide
  - Tab 5 mg with hydrochlorothiazide 12.5 mg
- Quinapril with hydrochlorothiazide
  - Tab 10 mg with hydrochlorothiazide 12.5 mg
  - Tab 20 mg with hydrochlorothiazide 12.5 mg
- Candesartan cilexetil
  - Tab 4mg
  - Tab 8 mg
  - Tab 16 mg
  - Tab 32 mg
- Losartan potassium
  - Tab 12.5 mg
  - Tab 25 mg
  - Tab 50 mg
  - Tab 100 mg
- Losartan potassium with hydrochlorothiazide
  - Tab 50 mg with hydrochlorothiazide 12.5 mg

1.3 The Subcommittee considered that, as the following pharmaceuticals were not fully subsidised in the Pharmaceutical Schedule, and as they did not have a unique use within hospitals, they should only be available within a hospital for continuation of care, not for initiation:

- Perinopril
  - Tab 2 mg;
  - Tab 4 mg
- Trandolapril
  - Cap 1 mg;
  - Cap 2 mg
- Enalapril with hydrochlorothiazide
  - Tab 20 mg with hydrochlorothiazide 12.5 mg

1.4 The Subcommittee considered that the listing of captopril oral liquid, candesartan, losartan and losartan with hydrochlorothiazide in a national PML should be subject to restrictions that are in line with the restrictions on each of these products in the Pharmaceutical Schedule.

1.5 Members noted that the wording of the Special Authority restrictions for candesartan, losartan and losartan with hydrochlorothiazide in the Pharmaceutical Schedule were different, and considered that it would be useful to have these aligned where possible.

1.6 The Subcommittee noted that irbesartan is not widely used within hospitals and is not subsidised on the Pharmaceutical Schedule, and recommended that it not be included in a national PML.

2 Alpha-Adrenoceptor Blockers

2.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Alpha Adrenoceptor Blockers heading.

2.2 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

- Doxazosin
  - Tab 2 mg
  - Tab 4 mg
- Phenoxybenzamine hydrochloride
  - Cap 10 mg
  - Inj 50 mg per ml, 2 ml ampoule
- Terazosin
  - Tab 1 mg
  - Tab 2 mg
  - Tab 5 mg

2.3 The Subcommittee considered that further information was needed before a recommendation could be made on the listing of phentolamine mesilate in a national PML, and advised PHARMAC staff to consult with anaesthetists, cardiac theatre staff and intensive care units to determine the circumstances for which this is used in hospitals, and what the advantages of it over phenoxybenzamine are.

2.4 The Subcommittee considered that further information was needed before a recommendation could be made on the listing of prazosin hydrochloride in a national PML, and advised PHARMAC staff to consult with urologists. Members noted that prazosin is currently used for post-traumatic stress disorder, and that consulting psychiatrists would also be useful.

2.5 The Subcommittee considered that the terazosin starter pack (7 x 1 mg tablets and 7 x 2 mg tablets) did not need to be included in a national PML. Members also considered that it would not be necessary to include a 1 mg tablet in a national PML if the 2 mg terazosin tablet could be halved.

2.6 **Antiarrhythmics**

2.7 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Antiarrhythmics heading.

2.8 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

- Adenosine
  - Inj 3 mg per ml, 2 ml vial
  - Inj 3 mg per ml, 10 ml vial
  - Inj 10 mg per ml, 2 ml
- Ajmaline
  - Inj 5 mg per ml, 10 ml
- Amiodarone hydrochloride
  - Inf 50 mg per ml, 3 ml ampoule
  - Tab 100 mg
  - Tab 200 mg
- Atropine sulphate
  - Inj 600 µg, 1 ml
- Digoxin
  - Tab 62.5 mg
  - Tab 250 mg
  - Oral liq 50 µg per ml
  - Inj 250 µg per ml, 2 ml vial
- Disopyramide phosphate
  - Cap 100 mg
  - Cap 150 mg
- Flecainide acetate
  - Tab 50 mg
  - Tab 100 mg
  - Cap long-acting 100 mg
  - Cap long-acting 200 mg
  - Inj 10 mg per ml, 15 ml ampoule
- Mexiletine hydrochloride
  - Cap 50 mg
  - Cap 200 mg
- Propafenone hydrochloride
  - Tab 150 mg

2.9 The Subcommittee considered that further advice was required in relation to adenosine. Members recommended consulting with the Cardiac Society and electrophysiologists on the need for the 3 mg per ml, 10 ml and 10 mg per ml, 2 ml presentations, whether there is a safety risk with the 10 mg per ml, 2 ml presentation and whether restrictions on the use of these should apply.

2.10 The Subcommittee recommended that the use of ajamline should be restricted to cardiology units.

2.11 The Subcommittee noted that the atropine 1200 µg injection had recently been discontinued, and considered that it was not necessary to add this to a national PML. Members considered that further information was needed before making a recommendation on the listing of atropine prefilled syringes (500 µg, 5 ml prefilled syringe and/or 1000 µg, 10 ml prefilled syringe) in a national PML, and advised PHARMAC staff to seek feedback on this matter from anaesthetists.

2.12 Members noted that an oral liquid formulation of flecainide is required, and that this can be achieved either by an unregistered product made by a compound manufacturer in Ireland or by compounding flecainide tablets in Ora products. The Subcommittee noted that PHARMAC is working with several paediatric pharmacists on this issue.

2.13 The Subcommittee noted that lidocaine with glucose was not a commonly used product, and recommended that it not be listed in a national PML.

2.14 The Subcommittee noted that mexiletine hydrochloride had been discontinued previously, but that PHARMAC was looking to list another brand in the Pharmaceutical Schedule. Members considered that while it is not an essential treatment it would be useful to have listed in a national PML and the Pharmaceutical Schedule for pain, pregnancy and cardiac patients with a moderate priority.

2.15 Members recommended that PHARMAC also seek feedback from electrophysiologists on all of the products under the Antiarrhythmics heading.

3 Antihypotensives

3.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Antihypotensives heading.

3.2 The Subcommittee noted that midodrine hydrochloride (tab 2.5 mg and tab 5 mg) is widely used in DHB hospitals and is fully subsidised in the Pharmaceutical Schedule and recommended it be included in a national preferred medicines list (PML) without need for further prioritisation.

3.3 Members recommended that the listing of midodrine hydrochloride in a national PML be subject to restrictions on its use that are in line with the Special Authority restrictions for it in the Pharmaceutical Schedule.

4 Beta-Adrenoceptor Blockers

4.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Beta-Adrenoceptor Blockers heading.

4.2 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

- Atenolol
  - Tab 50 mg
  - Tab 100 mg
  - Oral liq 25 mg per 5 ml
- Carvedilol
  - Tab 6.25 mg
  - Tab 12.5 mg
  - Tab 25 mg
- Celiprolol
  - Tab 200 mg
- Esmolol hydrochloride
  - Inj 10 mg per ml, 10 ml vial
- Labetalol
  - Tab 50 mg
  - Tab 100 mg
  - Tab 200 mg
  - Tab 400 mg
  - Inj 5 mg per ml, 20 ml ampoule
- Metoprolol succinate
  - Tab long-acting 23.75 mg
  - Tab long-acting 47.5 mg
  - Tab long-acting 95 mg
  - Tab long-acting 190 mg
- Metoprolol tartrate
  - Tab 50 mg
  - Tab 100 mg
  - Tab long-acting 200 mg
  - Inj 1 mg per ml, 5 ml vial
- Nadolol
  - Tab 40 mg
  - Tab 80 mg
- Pindolol
  - Tab 5 mg
  - Tab 10 mg
  - Tab 15 mg
- Propranolol
  - Inj 1 mg per ml, 1 ml
  - Tab 10 mg
  - Tab 40 mg
  - Cap long-acting 160 mg
- Sotalol
  - Tab 80 mg
  - Tab 160 mg
  - Inj 10 mg per ml, 4 ml ampoule
- Timolol maleate
  - Tab 10 mg

4.3 Members noted that acebutolol is no longer subsidised in Pharmaceutical Schedule following discontinuation of the subsidised brand, and that it does not have a unique use within hospitals. The Subcommittee recommended that it not be listed in a national PML.

4.4 Members recommended that consideration be given to the listing of atenolol oral liquid in the Pharmaceutical Schedule.

4.5 The Subcommittee noted the August 2010 PTAC minute for bisoprolol fumarate, and noted that PHARMAC was considering listing this in the Pharmaceutical Schedule. The Subcommittee considered that bisoprolol should be added to a national PML if it is subsidised in the Pharmaceutical Schedule.

4.6 The Subcommittee noted that while some DHBs have used higher strengths of esmolol (inf 250 mg per ml, 10 ml ampoule), this had only been in circumstances where the 10 mg per ml, 10 ml vial was not available, and recommended that this higher strength not be included in a national PML.

4.7 Members considered that the listing of an oral liquid presentation of labetalol in a national PML would be useful, but not essential if atenolol was available. Members gave a medium priority to this recommendation.

4.8 The Subcommittee noted that there may be a need for a propranolol oral liquid, and recommended that PHARMAC staff seek further information from paediatricians on this issue.

5 Calcium Channel Blockers

5.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Calcium Channel Blockers heading.

5.2 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

- Amlodipine
  - Tab 5 mg
  - Tab 10 mg
- Felodipine
  - Tab long-acting 2.5 mg
  - Tab long-acting 5 mg
  - Tab long-acting 10 mg
- Isradipine
  - Cap long-acting 2.5 mg
  - Cap long-acting 5 mg
- Nifedipine
  - Cap 5 mg
  - Tab long-acting 10 mg
  - Tab long-acting 20 mg
  - Tab long-acting 30 mg
  - Tab long-acting 60 mg
- Nimodipine

- Tab 30 mg
- Inf 200 µg per ml, 50 ml vial

▪ Diltiazem hydrochloride
- Tab 30 mg
- Tab 60 mg
- Cap long-acting 120 mg
- Cap long-acting 180 mg
- Cap long-acting 240 mg
- Inj 5 mg per ml, 5 ml

▪ Perhexiline maleate
- Tab 100 mg

▪ Verapamil hydrochloride
- Tab 40 mg
- Tab 80 mg
- Tab long-acting 120 mg
- Tab long-acting 240 mg
- Inj 2.5 mg per ml, 2 ml ampoule

5.3 The Subcommittee noted that isradipine tab 2.5 mg is used to compound an oral liquid formulation if there is no amlodipine oral liquid or if the current brand of amlodipine cannot be used for this purpose, and recommended that it be included in a national PML in such a situation.

5.4 The Subcommittee discussed the need for nimodipine tablets to be listed in the Pharmaceutical Schedule. Members noted that availability in the community would reduce work for hospital pharmacies, but that as it is a relatively low volume product, community pharmacies might not have stock of this when needed.

5.5 Members noted that the twice-daily presentations of diltiazem capsules (90 mg and 120 mg) were no longer listed on the Pharmaceutical Schedule, but that some DHBs had kept these on their own formularies. The Subcommittee recommended that, for safety reasons, these two presentations should not be included in a national PML.

5.6 Members recommended that the listing of perhexiline maleate in a national PML be subject to restrictions on its use that are in line with the Special Authority restrictions for it in the Pharmaceutical Schedule.

6 Centrally-Acting Agents

6.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Centrally-Acting Agents heading.

6.2 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

▪ Clonidine
- Patch 2.5 mg, 100 µg per day
- Patch 5 mg, 200 µg per day
- Patch 7.5 mg, 300 µg per day

▪ Clonidine hydrochloride

- Tab 150 µg
- Inj 150 µg per ml, 1 ml ampoule
- Inj 1.5 mg per ml, 1 ml
- Inj 1.5 mg per ml, 2 ml
- Inj 1.5 mg per ml, 20 ml

▪ Methyldopa
- Tab 125 mg
- Tab 250 mg
- Tab 500 mg

6.3 The Subcommittee noted that guanethidine monosulphate was a formulary item in a minority of DHBs and, where it was, it had generally not been used in some time. The Subcommittee recommended that it not be included in a national PML.

7 Diuretics

7.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Diuretics heading.

7.2 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

▪ Bumetanide
- Tab 1 mg

▪ Furosemide (frusemide)
- Oral liq 10 mg per ml
- Tab 40 mg
- Tab 500 mg
- Inj 10 mg per ml, 2 ml ampoule
- Inf 10 mg per ml, 25 ml ampoule

▪ Mannitol
- Inf 10%, 1000 ml
- Inf 15%, 500 ml
- Inf 20%, 500 ml

▪ Amiloride hydrochloride with furosemide
- Tab 5 mg with furosemide 40 mg

▪ Amiloride hydrochloride with hydrochlorothiazide
- Tab 5 mg with hydrochlorothiazide 50 mg

▪ Amiloride hydrochloride
- Tab 5 mg
- Oral liq 1 mg per ml

▪ Spironolactone
- Tab 25 mg
- Tab 100 mg
- Oral liq 5 mg per ml

▪ Bendroflumethazide (bendrofluazide)
- Tab 2.5 mg
- Tab 5 mg

▪ Chloratalidone (chlorthalidone)

- Tab 25 mg
- Chlorothiazide
  - Oral liq 50 mg per ml
- Indapamide
  - Tab 2.5 mg
- Metolazone
  - Tab 5 mg

7.3 The Subcommittee noted that triamterene with hydrochlorothiazide is no longer subsidised in Pharmaceutical Schedule following discontinuation of the subsidised brand, and that it does not have a unique use within hospitals. The Subcommittee recommended that it not be listed in a national PML.

7.4 Members noted that PHARMAC was looking to list amiloride 5 mg tablets in the Pharmaceutical Schedule.

7.5 The Subcommittee noted that cyclopenthiazide 500 µg tablets are not in common use in DHB hospitals, and are not subsidised in the Pharmaceutical Schedule. The Subcommittee recommended not including it in a national PML.

7.6 Members noted that hydrochlorothiazide tablets, which are unregistered, have been used to compound an oral liquid formulation. Members noted that a registered oral liquid formulation of chlorothiazide is proposed for inclusion on a national PML, and that there is potential for prescriber confusion between the two agents. The Subcommittee recommended not listing hydrochlorothiazide tablets in a national PML.

7.7 The Subcommittee noted that metolazone 5 mg tablets are currently on the Discretionary Community Supply (DCS) list for long-term treatment of congestive heart failure. Members considered that PHARMAC should consider the listing of this product on the Pharmaceutical Schedule under similar restrictions to those applying to the DCS listing.

8 Lipid-Modifying Agents

8.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Lipid-Modifying Agents heading.

8.2 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

- Bezafibrate
  - Tab 200 mg
  - Tab long-acting 400 mg
- Gemfibrozil
  - Tab 600 mg
- Atorvastatin
  - Tab 10 mg
  - Tab 20 mg
  - Tab 40 mg
  - Tab 80 mg

- Pravastatin
  - Tab 10 mg
  - Tab 20 mg
  - Tab 40 mg
- Simvastatin
  - Tab 10 mg
  - Tab 20 mg
  - Tab 40 mg
  - Tab 80 mg
- Acipimox
  - Cap 250 mg
- Nicotinic acid
  - Tab 50 mg
  - Tab 500 mg
- Cholestyramine
  - Sachets 4 g
- Colestipol hydrochloride
  - Sachets 5 g
- Ezetimibe
  - Tab 10 mg
- Ezetimibe with simvastatin
  - Tab 10 mg with simvastatin 10 mg
  - Tab 10 mg with simvastatin 20 mg
  - Tab 10 mg with simvastatin 40 mg
  - Tab 10 mg with simvastatin 80 mg

8.3 The Subcommittee recommended that the listing of pravastatin in a national PML be subject to restrictions on its use that are in line with the Special Authority restrictions for it in the Pharmaceutical Schedule. Members noted that PHARMAC staff were currently reviewing the Special Authority restrictions for pravastatin.

8.4 The Subcommittee noted that rosuvastatin was not subsidised in Pharmaceutical Schedule, and that it does not have a unique use within hospitals. The Subcommittee recommended that it not be listed in a national PML.

8.5 The Subcommittee noted that some DHBs currently use docosahexenoic acid with eicosapentaenoic acid (omega-3 fatty acids) for augmentation of clozapine. The Subcommittee considered that further advice was required in relation to this, and referred it to the Mental Health Subcommittee for review.

8.6 The Subcommittee recommended that the listing of ezetimibe and ezetimibe with simvastatin in a national PML be subject to restrictions on their use that are in line with the Special Authority restrictions for them in the Pharmaceutical Schedule.

9 Nitrates

9.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Nitrates heading.

9.2 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and

recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

- Glyceryl trinitrate
  - Tab 600 µg
  - Oral spray 400 µg per dose
  - Patch 25 mg, 5 mg per day
  - Patch 50 mg, 10 mg per day
  - Inf 1 mg per ml, 5 ml
  - Inf 5 mg per ml, 10 ml
  - Inf 1 mg per ml, 50 ml
- Isosorbide mononitrate
  - Tab 20 mg
  - Tab long-acting 40 mg
  - Tab long-acting 60 mg

10 Other Cardiac Agents

10.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to ivabradine.

10.2 Member noted that ivabradine is not a registered medicine and has only been used in one centre for one patient. The Subcommittee recommended that it not be included in a national PML.

11 Other Cardiac Stimulants

11.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to levosimendan.

11.2 The Subcommittee recommended that levosimendan (inf 2.5 mg per ml, 5 ml vial and inf 2.5 mg per ml, 10 ml vial) be included in a national PML. Members considered that restrictions would need to apply to the use of levosimendan, but considered that further advice was needed before making a recommendation on such restrictions.

11.3 The Subcommittee requested that the Cardiovascular Subcommittee undertake a full evaluation of levosimendan to assist in determining appropriate restrictions for this agent.

12 Sympathomimetics

12.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Sympathomimetics heading.

12.2 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

- Adrenaline

- Inj 1 in 1,000, 1 ml ampoule
- Inj 1 in 10,000, 10 ml ampoule
- Inj 1 in 10,000, 10 ml syringe

▪ Dobutamine hydrochloride
- Inf 12.5 mg per ml, 20 ml vial

▪ Dopamine hydrochloride
- Inf 40 mg per ml, 5 ml ampoule

▪ Ephedrine
- Inf 30 mg per ml, 1 ml syringe
- Inf 30 mg per ml, 1 ml ampoule

▪ Isoprenaline
- Inj 200 µg per ml, 1 ml ampoule
- Inj 200 µg per ml, 5 ml ampoule

12.3 The Subcommittee noted the use of adrenaline prefilled syringes and considered that their use was probably limited to appropriate situations, and that as the availability of these would often be an integral part of hospitals resuscitation plans, it would be difficult to withdraw them.

12.4 Members noted that Waikato DHB has indicated use of adrenaline inj 1 mg per ml, 30 ml. The Subcommittee deferred making a recommendation on this formulation pending further on what it is used for, and whether there is a need for it (or a similar product) in a national PML. Members recommended seeking input from plastic surgery departments.

12.5 The Subcommittee recommended the listing of metaraminol in a national PML, but considered that further advice from anaesthetists would be required to determine which formulations were required.

12.6 The Subcommittee recommended the listing of noradrenaline in a national PML, but considered that further advice from intensivists and paediatric intensivists would be required to determine which formulations were required.

13 Vasodilators

13.1 The Subcommittee reviewed the information from DHB hospitals and PHARMAC in relation to products under the Vasodilators heading.

13.2 The Subcommittee noted that the following pharmaceuticals are commonly used in DHB hospitals and/or are fully subsidised in the Pharmaceutical Schedule and recommended they be included in a national preferred medicines list (PML) without need for further prioritisation:

▪ Alprostadil
- Inj 500 µg per ml, 1 ml ampoule

▪ Amyl nitrite
- Cap, 0.3 ml crushable

▪ Diazoxide
- Inj 15 mg per ml, 20 ml ampoule

▪ Hydralazine hydrochloride
- Tab 25 mg
- Inj 20 mg per ml, 1 ml

- Minoxidil
  - Tab 10 mg
- Papaverine hydrochloride
  - Inj 12 mg per ml, 10 ml ampoule
  - Inj 30 mg per ml, 1 ml vial
- Pentoxifylline (oxpentifylline)
  - Tab 400 mg
- Phenylephrine hydrochloride
  - Inj 10 mg per ml, 1 ml vial
- Sodium nitroprusside
  - Inj 50 mg, vial
- Ambrisentan
  - Tab 5 mg
  - Tab 10 mg
- Bosentan
  - Tab 62.5 mg
  - Tab 125 mg
- Milrinone
  - Inj 1 mg per ml, 10 ml
- Sildenafil
  - Tab 25 mg
  - Tab 50 mg
  - Tab 100 mg
- Iloprost
  - Inj 100 µg per ml, 0.5 ml
  - Nebuliser soln 10 µg per ml, 2 ml

13.3 The Subcommittee noted that hydralazine 25 mg tablets are currently on the Discretionary Community Supply (DCS) list for long-term treatment of congestive heart failure. Members considered that PHARMAC should consider the listing of this product on the Pharmaceutical Schedule under similar restrictions to those applying to the DCS listing, with consideration also given to making it available for refractory hypertension.

13.4 The Subcommittee recommended that PHARMAC give consideration to listing minoxidil in the Pharmaceutical Schedule. Members noted that this is an unregistered medicine.

13.5 The Subcommittee recommended that nicorandial not be listed in a national PML as it does not have a unique use within hospitals. However the Subcommittee noted the October 2010 Cardiovascular Subcommittee minutes that it could be useful in a small number of patients as an alternative to perhexiline and recommended that PHARMAC staff consult with cardiologists regarding its exclusion.

13.6 The Subcommittee recommended that the listing of sildenafil, ambrisentan and bosentan in a national PML be subject to restrictions on their use that are in line with the Special Authority restrictions for them in the Pharmaceutical Schedule.

13.7 The Subcommittee noted that sildenafil 20 mg tablet was not subsidised in the Pharmaceutical Schedule, and that it does not have a unique use within hospitals. The Subcommittee recommended that it not be listed in a national PML.

13.8 Members noted that there may be a place for oral PDE-5 inhibitors for Raynaud's disease, and recommended seeking further information from rheumatologists on this issue.

13.9 Members noted that there is some pre-surgical use of oral PDE-5 inhibitors, and considered that further advice was needed from cardiac surgeons and cardiothoracic anaesthetists on this issue before a recommendation could be made.

13.10 The Subcommittee recommended that the listing of iloprost nebuliser solution in a national PML be subject to restrictions on its use that are in line with the Special Authority restrictions for it in the Pharmaceutical Schedule, but that there should be no restrictions on the use of iloprost infusion.

14 Matters Arising

14.1 Members noted that the use of captopril oral liquid at Waikato hospital is predominantly for post-cardiac surgery use as a way to provide lower doses than through tablets.

14.2 The Subcommittee noted that IV formulations of both phentolamine and phenoxybenzamine are used in DHB hospitals, and recommended that both be included in a national PML, and considered that specific consultation on this would not be required.

14.3 The Subcommittee noted that PHARMAC staff will be seeking paediatrician feedback on the need for propranolol oral liquid, and noted that its major use appears to be for the treatment of haemangiomas.

14.4 The Subcommittee noted that PHARMAC staff will be seeking feedback on the need for adrenaline 1 mg per ml, 30 ml; members noted that this presentation is being used in burns units in Waikato and Counties-Manukau.

14.5 Members noted that sildenafil is often used in neonatal units for persistent pulmonary hypertension of the newborn (PPHN) and to assist weaning from inhaled nitric oxide. The Subcommittee recommended that provision for this use also be included in restrictions applying to sildenafil in a national PML.

14.6 The Subcommittee noted that nebulised iloprost is used post-mitral valve surgery, which is outside the scope of the community Special Authority restrictions. The Subcommittee recommended that provision for this use also be included in restrictions applying to iloprost nebuliser solution in a national PML.

Cardiovascular Subcommittee – 23 September 2011

15 Dronedarone for atrial fibrillation

Application

15.1 The Subcommittee reviewed a memorandum from PHARMAC staff regarding dronedarone (Multaq) for the treatment of non-permanent and permanent atrial fibrillation (AF).

Recommendation

15.2 The Committee recommended that consideration of dronedarone for both non-permanent and permanent AF for inclusion on a national PML or the Pharmaceutical Schedule be deferred until its safety and risk/benefit profile is clarified.

Discussion

15.3 The Subcommittee noted that at its October 2010 meeting, it had requested that dronedarone be formally reviewed on the basis that it was an amiodarone alternative with less efficacy but with a better safety profile given the significant adverse effects that can occur with long-term amiodarone use.

15.4 The Subcommittee noted that dronedarone is not registered in New Zealand but is approved in the United States, Europe and Australia for patients who currently have or had non-permanent AF. The Subcommittee noted that the FDA approval included a Risk Evaluation and Mitigation Strategy with the goal of preventing its use in patients with heart failure due to a greater than two-fold increase in the risk of death.

15.5 The Subcommittee noted the results of the ATHENA (Singh et al. N Engl J Med 2007; 357: 987-99) and ANDROMEDA (Køber et al. N Engl J Med 2008; 358: 2678-87) studies which suggested that dronedarone was of benefit for patients with non permanent AF, due to a significant reduction in cardiovascular hospitalisation or death from any cause, but not congestive heart failure due to a significant increase in mortality.

15.6 The Subcommittee noted that in January 2011, the US Food and Drug Administration (FDA) issued a safety communication following several case reports of hepatocellular liver injury and hepatic failure in patients treated with dronedarone, including two post-marketing reports of acute hepatic failure requiring transplantation.

15.7 The Subcommittee noted that in July 2011, the PALLAS Phase IIIb trial, which was investigating the use of dronedarone in patients with permanent AF (in an effort to expand its indication from non-permanent AF), had been discontinued following an observed significant increase in cardiovascular events in the dronedarone arm.

15.8 The Subcommittee noted that as a result of the severe liver injury reports and the results of the PALLAS study, the European Medicines Agency (EMA) is reviewing dronedarone's risk/benefit profile.

15.9 The Subcommitee noted that while Sanofi considers that the benefit-risk of dronedarone remains unchanged in non-permanent AF, it is examining the trial

databases in an effort to clarify the adverse effects profile and is not intending to seek registration in New Zealand, provide compassionate supply for patients, or seek a listing on the Pharmaceutical Schedule until the risk-benefit profile has been examined.

15.10 The Subcommittee considered that the PALLAS trial results suggested that dronedarone should not be used in permanent AF and while the ATHENA trial results suggested that it is appropriate for non-permanent AF the toxicity issues were an outstanding concern

16 Other Pharmaceuticals

16.1 The Subcommittee reviewed a series of recommendations by the Hospital Pharmaceuticals Subcommittee in regards to which pharmaceuticals relevant to cardiology should be included in a national PML. The Subcommittee also reviewed the responses and comments on the draft recommendations that PHARMAC had received from relevant colleges and professional societies.

Alpha-Adrenoceptor Blockers

16.2 In relation to prazosin, the Subcommittee noted that it had been unavailable recently and recommended that it is only included in a national PML if it is listed in section B of the Pharmaceutical Schedule.

Antiarrhythmics

16.3 In relation to adenosine, the Subcommittee considered that:

- Inj 3 mg per ml, 2 ml vial (6 mg in 2 ml) should be included in a national PML as it is used in emergency departments.
- Inj 3 mg per ml, 10 ml vial (30 mg in 10 ml) should be included in a national PML, but should be restricted to cardiac catheterisation (CATH) and electrophysiology (EP) labs only – it should not be found on emergency department shelves.
- Inj 10 mg per ml, 2 ml vial (20 mg in 2 ml) was not required on a national PML.

16.4 In relation to ajmaline, the Subcommittee agreed with the recommendation that its use is limited to within cardiology/coronary care units.

16.5 In relation to atropine, the Subcommittee supported its listing in a national PML, and considered that the ampoules, rather than pre-filled syringes, would be acceptable.

16.6 In relation to flecainide tablets the Subcommittee recommended that consideration be given to not including the 100 mg tablet on a national PML and to delisting it from Section B of the Pharmaceutical Schedule as it can be confused with the 100 mg long-acting capsules presentation resulting in prescribing and dispensing errors much the same as occurred with the different diltiazem presentations. The Subcommittee noted that the short-acting flecainide tablets may be used as a pill-in-the-pocket for infrequent paroxysmal atrial fibrillation and that the 100 mg tablet would be useful in that setting but considered that the 50 mg tablet would remain available. The Subcommittee recommended retaining the 50 mg tablet and the

long-acting preparations in Section B of the Pharmaceutical Schedule and listing them on a national PML.

16.7 In relation to lignocaine with glucose infusions, the Subcommittee supported the recommendation to exclude them from a national PML. The Subcommittee noted that there would be a need for lignocaine with glucose ampoules, which were not considered by the Hospital Pharmaceuticals Subcommittee.

16.8 In relation to mexiletine hydrochloride, the Subcommittee noted that this was used for a very small niche patient group to prevent malignant ventricular arrhythmia, which could be up to perhaps 8 patients, as well as for some patients with pain during pregnancy. The Subcommittee recommended that PHARMAC staff source a brand for listing in Section B of the Pharmaceutical Schedule and the national PML.

Centrally Acting Agents

16.9 In relation to guanethidine monosulphate, the Subcommittee supported the recommendation to exclude it from a national PML.

Diuretics

16.10 The Subcommittee reiterated its previous comments that amiloride 5 mg tablets should be listed on the Pharmaceutical Schedule.

16.11 In relation to metolazone, the Subcommittee noted that it is currently listed on the Discretionary Community Supply (DCS) list and that outpatient use is rare but recommended that it is listed in Section B of the Pharmaceutical Schedule and the national PML for use in "patients with refractory heart failure who are unresponsive to Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs) and diuretics".

Other Cardiac Agents

16.12 The Subcommittee noted that ivabradine is used in the treatment of angina, congestive heart failure and sinus tachycardia. The Subcommittee noted that the clinical evidence for ivabradine in congestive heart failure was not impressive but considered that ivabradine should be listed on the national PML for the treatment of sinus tachycardia in patients who have failed treatment with other pharmaceutical agents and that its use should be limited to Cardiologists only. The Subcommittee recommended that if ivabradine is listed on the national PML then it should be listed in Section B of the Pharmaceutical Schedule and that both the national PML listing and a Section B listing would be with a low priority.

16.13 In relation to ranolazine, the Subcommittee noted that it is in development and may have a place as an alternative to amiodarone.

Vasodilators

16.14 In relation to hydralazine, the Subcommittee noted that it is currently listed on the DCS list. The Subcommittee noted that it is an old drug and if more widely available would only have a small usage. The Subcommittee considered that it should be listed in Section B of the Pharmaceutical Schedule for use in refractory hypertension and (when used in combination with a nitrate) for ACE Inhibitor/ARB

intolerant heart failure patients. The Subcommittee considered that it could be restricted to the above patient groups or open listed if usage was small.

16.15 In relation to sildenafil, the Subcommittee considered that access to it could be widened although the Subcommittee noted that overseas data indicated that a high number of PAH diagnosis were incorrect and that wider access could have an effect on the demand for iloprost and bosentan.

16.16 In relation to minoxidil, the Subcommittee had no objection to it being listed in Section B of the Pharmaceutical Schedule and noted that it would have very little use.

16.17 In relation to nicorandil, the Subcommittee considered that it should be listed on the Pharmaceutical Schedule with a medium priority and with the current perhexiline access criteria. The Subcommittee noted that usage would be low as it would be an alternative to perhexiline and there are only a small number of patients on perhexiline.

17 Levosimendan for the short-term treatment of acutely decompensated chronic heart failure

Application

17.1 The Committee reviewed a memorandum from PHARMAC staff in regards to levosimendan in acute decompensated chronic heart failure.

Recommendation

17.2 The Subcommittee recommended that levosimendan be included on the national PML with a low priority and with tight restrictions. The Subcommittee recommended that if listed, levosimendan should be restricted to patients awaiting a heart transplant or following cardiac surgery although an opinion from a heart failure and heart transplant specialist should be obtained.

Discussion

17.3 The Subcommittee noted that levosimendan is indicated for short-term treatment of acutely decompensated chronic heart failure in situations where conventional therapy is not sufficient, and in cases where inotrophic support is considered appropriate.

17.4 The Subcommittee considered that levosimendan would be a last-line treatment in a patient group with a desperate need and that the mortality endpoint and not the surrogate endpoints were of interest.

17.5 The Subcommittee noted that alternative options included no treatment, milrinone or dobutamine - which have a number of additional indications.

17.6 The Subcommittee noted that levosimendan has a unique dual action as it enhances the sensitivity of the heart to calcium while also opening potassium channels.

17.7 The Subcommittee noted literature reviews (Mathieu and Craig. JICS 2011; 12(1): 15-24 and De Luca et al. Eur Heart J 2006; 27: 1908-1920), meta-analyses (Delaney et al. International Journal of Cardiology 2010; 138: 281-289, Landoni et

al. Minerva Anestesiol 2010; 76: 276-86 and Landoni et al. J of Cardiothoracic and Vascular Anesthesia 2010; 24(1): 51-57), an editorial (Omerovic et al. European Journal of Heart Failure 2010; 12: 313-314) and a number of studies including:

- LIDO (Follath et al. Lancet 2002; 360: 196-202) – levosimendan improved heamodynamic endpoints and reduced mortality when compared with dobutamine.
- CASINO (2004) – an unpublished study in which levosimendan showed a mortality benefit when compared with dobutamine or placebo.
- REVIVE II (2006) – an unpublished study in which levosimendan improved symptoms but trended towards higher mortality compared to placebo.
- SURVIVE (Mebazaa et al. JAMA 2007; 297: 1883-1891) – levosimendan showed a non-statistically significant trend to reduced mortality compared with dobutamine.

17.8 Overall, the Subcommittee considered the quality of evidence for levosimendan to be poor, good for dobutamine and that there was very little reported evidence for milrinone. However, the Subcommittee did consider that it was a very difficult area to do high quality trials.

17.9 The Subcommittee considered that mechanistic studies in animal models showed that levosimendan improved a range of surrogate endpoints which are associated with improved prognosis, that early small clinical studies confirmed these results but later larger clinical studies comparing levosimendan with dobutamine did not demonstrate a superiority of levosimendan over dobutamine.

17.10 The Subcommittee considered that one advantage of levosimendan over other treatments was that it enabled some patients to be discharged instead of remaining in hospital.

17.11 The Subcommittee considered that levosimendan should not be used in all heart failure patients but that it could be useful in selected patient groups, namely patients awaiting a heart transplant or following cardiac surgery.

Hospital Pharmaceuticals Subcommittee – 6 March 2012

18 Review of Cardiovascular System Recommendations

18.1 The Subcommittee reviewed its previous recommendations in relation to products in the Cardiovascular System group, feedback from other organisations such as the Cardiac Society and the Paediatric Society, and recommendations from the Cardiovascular Subcommittee.

18.2 Members noted that antithrombotic agents will be revisited later after the Haematology Subcommittee has had the opportunity to comment on agents in this section.

Agents Affecting the Renin-Angiotensin System

18.3 The Subcommittee noted some feedback that requested access to combined ACE/ARB treatment. Members noted that while this was not currently available for candesartan, it was possible for losartan as there are now no prescribing restrictions on this product. Members also noted that PTAC considered this issue at its May 2009 meeting and noted that combined ACE/ARB treatment does not appear to provide additional benefits and may result in an increase in adverse events.

Alpha-Adrenoceptor Blockers

18.4 The Subcommittee noted that no feedback was received from urologists on the need for prazosin, but recommended that prazosin be listed in a national PML as it is subsidised in the Pharmaceutical Schedule.

Antiarrhythmics

18.5 The Subcommittee noted that the Cardiovascular Subcommittee considered that a 20 mg presentation of adenosine was not required in hospitals, and recommended that this be excluded from a national PML.

18.6 The Subcommittee noted the comment from the College of Anaesthetists that atropine is no longer recommended as part of resuscitation protocols, and recommended that atropine prefilled syringes be excluded from a national PML.

Beta-Adrenoceptor Blockers

18.7 Members noted that Paediatric Society indicated that an oral liquid form of labetalol is not required, but that a liquid form of propranolol is important. The Subcommittee recommended that propranolol oral liquid (1 mg per ml) be included in a national PML.

18.8 Members noted that bisoprolol is to be listed in the Pharmaceutical Schedule from April 2012 and recommended that it be included in a national PML.

Calcium Channel Blockers

18.9 The Subcommittee noted that a 2.5 mg tablet of amlodipine was now subsidised in the community, and that this would subsequently be included in a national PML.

18.10 The Subcommittee noted that isradipine 2.5 mg tablets are used to compound an oral liquid at Starship, and recommended that this be included in a national PML.

18.11 Members noted feedback that requested that nicardipine be included for use in the ICU setting. The Subcommittee considered that a submission for this should be requested, and provided to PTAC for consideration.

Diuretics

18.12 The Subcommittee noted and agreed with the recommendation from the Cardiovascular Subcommittee on the listing of metazolone in the community. The Subcommittee considered that prescribing restrictions would not be necessary in hospitals and that it would be low risk in the community.

Lipid-Modifying Agents

18.13 Members noted that the Special Authority restriction for pravastatin had been removed, and that this would be reflected in a national PML.

18.14 The Subcommittee continued to defer a recommendation in relation to Omega-3 fatty acids, pending feedback from the Mental Health Subcommittee.

Other Cardiac Agents

18.15 The Subcommittee noted that the Cardiovascular Subcommittee had recommended that levosimendan be included in a national PML with a low priority. The Subcommittee recommended that further views be sought from cardiac intensivists and paediatric intensivists.

18.16 Members noted the Cardiac Society had highlighted ivabradine, dronaderone and vernakalant in its response. The Subcommittee considered that these agents would need to undergo a full evaluation by PTAC.

Sympathomimetics

18.17 The Subcommittee noted that it had previously deferred making a recommendation on adrenaline 1 mg per ml, 30 ml injection. Members noted that this is used in burns units at Waikato and Counties-Manukau to soak dressings during skin grafts. The Subcommittee recommended that this presentation be included in a national PML.

18.18 The Subcommittee noted the feedback in relation to noradrenaline, and recommended that the following presentations be included in a national PML:

- 0.06 mg per ml, 50 ml syringe
- 0.06 mg per ml, 100 ml bag
- 0.1 mg per ml, 100 ml bag
- 0.12 mg per ml, 50 ml syringe
- 0.12 mg per ml, 100 ml bag
- 0.16 mg per ml, 50 ml syringe
- 1 mg per ml, 2 ml ampoule
- 1 mg per ml, 100 ml bag

18.19 The Subcommittee noted that it would be appropriate to eventually reduce the number of presentations in use, and recommended that PHARMAC undertake such work in the future.

Vasodilators

18.20 The Subcommittee noted the recommendation by the Cardiovascular Subcommittee to subsidise hydralazine in the community.

18.21 The Subcommittee noted feedback from the Cardiac Society on the use of iloprost nebuliser solution, and recommended that restrictions for this in a national PML be extended to include the following indications:

- use in catheter laboratories for diagnosing reversibility of PAH; and
- use following mitral or tricuspid valve surgery.

18.22 The Subcommittee noted feedback in relation to sildenafil, highlighting current use in cardiac surgery and a potential use in Raynaud's phenomenon. Members considered that both of these indications should be reviewed by PTAC.

18.23 The Subcommittee noted the recommendation from the Cardiovascular Subcommittee to list nicorandil in the Pharmaceutical Schedule with a medium priority. Members considered that PTAC would need to be provided with some supporting evidence for this product.

Pharmacology and Therapeutics Advisory Committee – 10 & 11 May 2012

19 Hospital Pharmaceuticals Review

19.1 The Committee considered a list of pharmaceuticals under consideration for use in DHB hospitals under the Cardiovascular System heading, including advice from the Hospital Pharmaceuticals Subcommittee and the Cardiovascular Subcommittee. Except where indicated, the Committee agreed with the recommendations by the subcommittees.

19.2 The Committee recommended that the restriction for adenosine 3 mg per ml, 10 ml injection, should include MRI as it is used in this setting for stress testing.

19.3 The Committee noted that labetalol oral liquid had not been recommended for inclusion in a national Preferred Medicines List (PML) as it is not funded in the community, and it was not considered to be required from a paediatric perspective. Members noted that labetalol is often used in patients following ischaemic stroke, and considered that an oral liquid form may be beneficial for patients with a nasogastric tube, but that alternatives may be available. The Committee considered that it would be important for PHARMAC staff to ensure that this issue is considered as part of the consultation on this section.

19.4 Members noted that it had been requested that nicardipine, dronaderone, ivabradine and vernakalant be available in DHB hospitals and subsidised in the community. The Committee considered that it would need to consider funding applications before making any recommendations on these products.

19.5 The Committee noted that the Hospital Pharmaceuticals Subcommittee had recommended that minoxidil be included in a national PML, and that it also be considered for listing in the community. The Committee considered that there is very little use of this product and questioned the need for it. It considered that it would not be appropriate to list minoxidil in a national PML if it was not funded in the community, and considered that there was not a significant unmet need for this product although this should be considered in the forthcoming public consultation on this section.

19.6 The Committee noted that there had been requests for sildenafil to be available in DHB hospitals for use in cardiac surgery patients. The Committee considered that it would need to consider evidence in support of this use, and requested that PHARMAC staff source an application for this indication.

19.7 The Committee noted that the Cardiovascular Subcommittee had recommended that nicorandil be subsidised in the community and included in a national PML. Members considered that the Committee would prefer to review an application

19.8 The Committee noted that the Cardiovascular Subcommittee had recommended that levosimendan be included on the national PML with a low priority and with tight restrictions – being patients awaiting a heart transplant or following cardiac surgery, although an opinion from a heart failure and heart transplant specialist should be obtained.

19.9 The Committee noted that PHARMAC staff had obtained additional views including current DHB treatment protocols.

19.10 The Committee noted that in clinical trials comparing levosimendan with placebo and also to dobutamine, that levosimendan has been shown to improve haemodynamics but that evidence that it decreases mortality rates is not clear.

19.11 The Committee noted REVIVE II, a study which did not show a mortality benefit, has not been published and that SURVIVE (Mebazaa et al. JAMA 2007;297:1883-1891) did not show a significant mortality benefit over dobutamine.

19.12 The Committee noted that in the cardiac surgery setting levosimendan has been shown to decrease the risk of post surgical heart failure but that this does not necessarily result in early discharge form hospital or an improvement in mortality rates when compared with usual care (Lehmann et al. Critical Care Medicine 2011;39:2365-6; Lahtinen et al. Critical Care Medicine 2011;39:2263-70).

19.13 The Committee noted that some hospital protocols allowed the use levosimendan in decompensated heart failure if the patient is being treated with a beta-blocker. The Committee considered that dobutamine could still be used in these patients although the dose may need to be increased to compensate for the effect of the beta-blocker.

19.14 The Committee recommended that levosimendan be included in a national PML, and restricted to the following uses:

19.14.1 As a bridge to heart transplant, in patients who have been accepted for transplant.

19.14.2 For the treatment of heart failure following heart transplant.

19.14.3 For the treatment of severe acute decompensated heart failure that is non-responsive to dobutamine. Prescribing to be by, or under the recommendation of, an intensivist or a cardiologist.