National Prescribing Service Limited

Drug Utilisation Briefing

for

Enhanced Divisional Quality Use of Medicines Program

November 2006

Target drug group:	Cardiovascular lipid-modifying drugs
NPS related program: (date of delivery)	Management of dyslipidaemia (2002)

NPS is an independent, non-profit organisation for Quality Use of Medicines,
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Contents

Suggested citation for this document

National Prescribing Service. Drug utilisation briefing for Enhanced Divisional Quality Use of Medicines program: Cardiovascular. Lipid-modifying drugs. October 2006.

1. Clinical practice guidelines

- Australian Medicines Handbook. 2006 [1]
- National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Position Statement on Lipid Management-2005 [2]

  http://www.heartfoundation.com.au/downloads/Lipids_HLCPosStatementFINAL_2005.pdf
- Therapeutic Guidelines: Cardiovascular. 2003 [3]
- National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Lipid Management Guidelines — 2001. Addendum Oct 2002. [4]

  http://www.heartfoundation.com.au/index.cfm?page=45

Summaries provided in NPS resources (see below).

2. NPS resources

Resources are available via the NPS website at www.nps.org.au Print copies available on request. Resources marked with an asterisk are only available to divisions of general practice with NPS facilitators for use within their NPS Program, and therefore not available via the NPS website.

- Case studies including results and expert commentaries
  - 38: Management of ischaemic heart disease (August 2005)
  - 19: Dyslipidaemia and coronary heart disease risk (February 2002)
- Clinical audits
  - Optimising drug use in ischaemic heart disease (2005)
  - Dyslipidaemia and coronary heart disease risk (2002)
- *Divisional Case Scenarios for small group case meetings (2002)
  - 26 and 27: Management of dyslipidaemia.
- Heart Protection Study in perspective (August 2002) with further information for GPs and for *NPS facilitators.
- Indicators of quality prescribing manual (2006)
- **Management of dyslipidaemia* program (June 2002)
  - Background materials
  - Practice Visits Program detailing card with summary of guidelines and comparative information on lipid-modifying drugs
- NPS News 20 (February 2002)
- NPS RADAR
  - New indications for ezetimibe (Ezetrol) and ezetimibe with simvastatin (Vytorin) (April 2006)
  - Review of fenofibrate (Lipidil) updated with FIELD study evidence (April 2006)
  - Atorvastatin (Lipitor) for the management of lipid disorders (December 2005)
  - Review of ezetimibe (Ezetrol) for dyslipidaemia (August 2004)
- Prescribing Practice Reviews
  - 31: Ischaemic heart disease (August 2005)
  - 17: Managing dyslipidaemia (February 2002)
- Prescribing software guides
  - Review concurrent prescribing of beta blockers, antiplatelet agents (or anticoagulants), and statins in myocardial infarction. Instructions for Medical Director software (2006)
  - Using prescribing software to assist in reviewing your prescribing of lipid-modifying drugs. Instructions for Locum 3, Genie, Medical Director and Medical Spectrum software (2002)

- PBS prescribing data feedback in PPR 17 (February 2002)
- Patient education material: Managing dyslipidaemia and cardiovascular disease with lifestyle interventions (February 2002).

3. What's what: lipid-modifying drugs

Table 1: Lipid-modifying drugs currently on the Pharmaceutical Benefits Scheme

Drug group	Generic name	Strengths available	Brand name	PBS codes
HMG-CoA reductase inhibitors [statins]	atorvastatin	10, 20, 40, 80 mg	Lipitor	8213G, 8214H, 8215J, 8521L
	fluvastatin	20, 40 mg	Lescol, Vastin,	8023G, 8024H
	pravastatin	10, 20, 40, 80 mg	Pravachol, Lipostat, Liprachol	2833D, 2834E, 8197K, 8829Q
	simvastatin	5, 10, 20, 40, 80 mg	Lipex, Zimstat, Zocor	2013Y, 2011W, 2012X, 8173E, 8313M
Fibrates	fenofibrate	48, 67, 145, 160 mg	Lipidil	9022W, 8721B, 9023X, 8722C
	gemfibrozil	600 mg	Ausgem, Gemfibrozil, Jezil, Lipazil, Lopid	1453L
Bile acid sequestrants	cholestyramine	4, 8 g of cholestyramine	Questran Lite	2967E, 2978R
	colestipol	5 g	Colestid	1224K
Other lipid modifying agents	ezetimibe	10 mg	Ezetrol	8757X
Lipid modifying agents, combinations	ezetimibe with simvastatin	10/40 mg 10/80 mg	Vytorin	8881K 8882L

Refer to the *Schedule of Pharmaceutical Benefits for Approved Pharmacists and Medical Practitioners* for PBS authority requirements and restricted benefit listings.
http://www.health.gov.au/internet/wcms/publishing.nsf/Content/Schedule+of+Pharmaceutical+Benefits-1

http://www.health.gov.au/internet/wcms/publishing.nsf/content/509606805EFDD713CA2571E1000E03CD/$File/Lipid%20lowering%20drugs.pdf.

Table 2: Other drugs / agents used for lipid-modifying therapy

Nicotinic acid*	Nicotinic acid	250 mg	Nicotinic Acid (generic only)	Not available on the PBS
Complementary therapies for dyslipidaemia	Fish oils (omega-3 fatty acids - EPA, DHA)	1 g capsules contain 300mg omega-3 fatty acids (180 mg EPA and 120 mg DHA)		
	Plant sterols and stanols			
	Policosanol			

*Last PBS listed in August 2005

4. Definitions used in this document

Lipid-modifying drugs

HMG-CoA reductase inhibitors [statins] (atorvastatin, fluvastatin, pravastatin, simvastatin); fibrates (fenofibrate, gemfibrozil); bile acid sequestrants (cholestyramine and colestipol); other lipid modifying agents (ezetimibe); lipid modifying agent combinations (ezetimibe with simvastatin) and nicotinic acid.

Higher absolute risk of coronary heart disease

As defined in Table 1 of the Lipid Management Guidelines. [4]

Known coronary heart disease (CHD)

History of myocardial infarction (MI) or angina.

5. What do we currently know about the prescribing of lipid-modifying drugs?

The Lipid Management Guidelines: [4]

state

- there is strong evidence that lipid-modifying treatment reduces CHD progression, morbidity and mortality for people at high risk of CHD events;
- treating those at highest risk to lower plasma lipid levels has been shown to be cost effective;
- however, despite the potential for significant health gain, information from overseas and Australia shows that effective lipid-modifying therapies are significantly underused.

advocate a change in emphasis for treatment decisions

- treatment decisions should be based on a patient's estimated "absolute CVD risk"- the probability of developing CVD over a specific time period- rather than on blood lipid levels.

Evidence of benefits of lipid-modifying therapy

Secondary prevention

- Lipid-modifying therapy has greatest benefits for those at greatest absolute risk of CHD. In the 4S [5,6], CARE [7], LIPID [8], and HPS [9] trials, patients with CHD had their absolute risk of CHD death or non-fatal MI reduced by up to 9% over five years by *simvastatin or pravastatin* over a wide range of plasma-cholesterol concentrations (4–8 mmol/L). A similar but less conclusive trend was achieved with gemfibrozil in the VA-HIT study. [10]

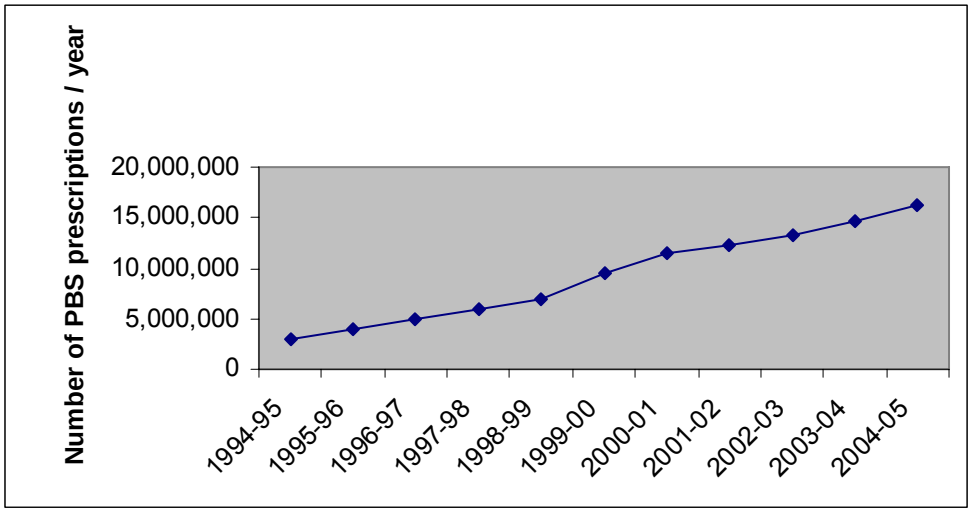
Primary prevention

- The CARDS trial [11] which was a primary prevention study in patients with type 2 diabetes, showed that there was a relative risk reduction of 37% in major cardiovascular events with *atorvastatin* vs placebo. The ASCOT-LLA [12] (*atorvastatin* vs placebo) assessed the effect of lipid lowering in the primary prevention of CHD in hypertensive patients who are not conventionally deemed dyslipidaemic and similarly showed a significant 36% reduction in the relative risk of the primary endpoints (non-fatal MI and fatal CHD). Evidence from the other principal primary prevention trials—WOSCOPS [13], AFCAPS/TexCAPS [14], and the Helsinki Heart Study [15, 16] —is not as persuasive as that from the secondary prevention trials.[17] These trials have not shown any difference in overall mortality between those taking lipid-modifying drugs and those who were not.[17]
- Study results indicate that approximately three times as many people without CHD need to be treated for five years to prevent one CHD event as people with CHD.[17]

Management of lipid disorders has increased significantly over the last decade but are lipid disorders being managed appropriately?

- The management rate of lipid disorders continues to increase, indicating an increasing prevalence of hypercholesterolaemia in the Australian population. This increase is accompanied by a continued growth in prescriptions for lipid-lowering medications, specifically the statins.[18]
- In 2004–05, lipid disorder:
  - was the fifth most common problem managed in general practice, and
  - accounted for 2.1% of all problems managed.[18]
- Management of lipid disorder increased significantly from 1998/99 (2.5 per 100 encounters) to 2004/05 (3.3 per 100 encounters, p<0.0001).[18]
- The rate of statins prescribed or supplied increased from 1.9 medications per 100 encounters in 1998–99 to 3.3 per 100 encounters in 2004–05 (p<0.0001). Atorvastatin prescribing increased from 0.9 per 100 encounters in 2000-01 to 1.4 per 100 encounters in 2004-05 (p<0.0001). However, the increase in lipid medications was entirely explained by the increase in the management rate of lipid disorders. There was no significant change in the rate of statins prescribed or supplied for management of lipid disorder problems. Since 1998–99 they have been prescribed/supplied at about 61 medications per 100 lipid disorder problems (p=0.71).[18]
- The usage of lipid-modifying drugs on the PBS has increased from just over 2 million prescriptions in 1991/92 to nearly 16 million prescriptions in 2004/05.[19]
- There has been a 19% increase in PBS volume of lipid-modifying drugs over the period 2002-03 to 2004-05.[20,21]

Figure 1: National trend in volume of PBS prescriptions for lipid modifying drugs 1994-95 to 2004-05



- The PBS dataset does not identify the <u>appropriateness</u> of the prescribing of lipid-modifying drugs i.e. whether lipid-modifying drugs are being used in appropriate patients, if appropriate monitoring is performed and whether target lipid levels are achieved.
- Results from an Australian study showed that the prescribing of lipid-lowering therapy for secondary prevention is suboptimal.[22] The study participants were 352 patients admitted to hospital with acute MI or unstable angina.
  - total serum cholesterol levels exceeded 5.5 mmol/L in 25% of the patients who had been taking lipid-modifying therapy at time of hospital admission (N.B. lower target of 3.5 mmol/L now advised [1] which differs from PBS criteria and other guidelines);

- 18% of patients with a total cholesterol >5.5 mmol/L and 34% of patients with total cholesterol > 4 mmol/L did not receive a prescription for a lipid modifying drug on discharge;
- at follow-up, 70% of patients discharged without therapy had not been commenced on lipid modifying therapy by their GPs;
- compliance in those discharged on lipid modifying therapy was 88%, suggesting that commencing treatment in hospital is likely to result in continuing therapy in the community (although it was recognised that, as this was patient reported compliance, there was a risk of over-reporting).

The high discontinuation rates of lipid-modifying drug therapy are a concern

- Results showing benefits of lipid-modifying therapy in primary and secondary prevention of CHD from various clinical trials were achieved with high levels of patient compliance, whereas, an Australian study evaluating apparent discontinuation rates in patients newly prescribed lipid-lowering drugs reported that 60% of patients had discontinued treatment over 12 months with 50% of the apparent discontinuations occurring within three months starting treatment. [21] The reasons for discontinuation included patients being unconvinced about need for treatment, poor efficacy and adverse events. The authors concluded that this high apparent discontinuation rate suggests significant wastage of resources in treatments that are initiated but not continued and a lost opportunity for heart disease prevention. Similarly an Australia-wide assessment of discontinuation rates in patients newly prescribed lipid lowering drugs found that 7-9 months after treatment initiation discontinuation rates averaged 30%. [24]

6. Principles of quality prescribing – lipid-modifying drugs

Judicious selection of management options

- Do <u>not</u> prescribe lipid-modifying drugs to patients who do *not* have a higher absolute risk of CHD as defined by the Lipid Management Guidelines.[4]
- Manage other modifiable cardiovascular risk factors in all patients at higher absolute risk of CHD e.g. hypertension, diabetes, smoking cessation, body weight reduction, increased physical activity.[4]
- Treat secondary causes of dyslipidaemia, e.g. obesity, diabetes, hypothyroidism, obstructive liver disease, nephrotic syndrome, excess alcohol intake.[17]
- Use lipid-modifying drugs in association with dietary and lifestyle measures in all patients. [4]

Appropriate choice of medicines, where a medicine is considered necessary

The Lipid Management Guidelines should be referred to for recommendations on the appropriate use of lipid-modifying therapy including drug therapy. [4]

- Use lipid-modifying drugs in conjunction with dietary therapy, in people with known CHD (a history of MI or angina), who have a total cholesterol level > 3.5 mmol/L.[1]
- Consider lipid-modifying drugs for people at higher absolute risk of CHD whose lipid levels have remained above target levels (total cholesterol > 3.5 mmol/L) after a 6 week trial of dietary therapy.[1] Eligibility for subsidy of lipid-modifying drugs will depend on meeting the PBS criteria for subsidy. [25,26]
- Statins are the drug of choice if hypercholesterolaemia is predominant (statins are the most effective LDL-C lowering agents with typical reductions of 30-50%).[1,4]
- Atorvastatin is more potent at lowering plasma cholesterol levels compared with simvastatin and pravastatin (across its dose range atorvastatin reduces LDL–C about 5–20% more than the reductions achieved with simvastatin or pravastatin). If existing treatment with simvastatin or pravastatin achieves target cholesterol levels, it is not necessary to switch to a more potent statin. [27]
- Atorvastatin reduces plasma triglyceride levels more than simvastatin; simvastatin elevates plasma HDL–C levels more than atorvastatin. [27]
- Fibrates are the drug of choice if hypertriglyceridaemia is predominant (reduce triglycerides by 40-80%) along with low a HDL-C.[1,4]

- Use ezetimibe for combination therapy with a statin for people who have CHD or diabetes and whose cholesterol levels are inadequately controlled by a statin and as monotherapy for people, who are unable to take statins due to contra-indications or clinically-important adverse effects, and people with homozygous sitosterolaemia. [1]
- Consider combination drug therapy for mixed hyperlipidaemia or high-risk people whose lipid profile remains unacceptable after a trial on monotherapy. In general a specialist should initiate such therapy.

Safe and effective use of medicines

- Titrate the statin dose upwards from the initial starting dose every 4-6 weeks to move towards target lipid levels. [1]
- Prescribe the minimum effective dose. The optimum dose for statins is uncertain [4], however, more than 80% of the reduction in LDL-C is achieved with 50% of the maximum dose and the risk of hepatotoxicity and myotoxicity increases as the dose of statin increases (maximum doses: atorvastatin 80 mg daily, fluvastatin 40 mg twice daily, pravastatin 80 mg daily, simvastatin 80 mg daily). The recommended daily dose of ezetimibe in adults and children 10 years and over is 10 mg. [1]
- Assess liver enzymes before commencing statin therapy, at 3 months and then if the dose is increased at the 6 monthly renewal of prescription and if the patient has signs of liver toxicity. [1]
- Any movement towards target cholesterol levels should be beneficial even if they are not reached. Recommended target levels primarily for people at higher absolute risk are:[1, 2]
    - Total cholesterol <3.5 mmol/L LDL-C <2.0 mmol/L
    - HDL-C >1.0 mmol/L Triglycerides <1.5 mmol/L
- Assess patient's compliance with therapy (lifestyle, dietary and drug therapy) at each visit as a high level of patient compliance with therapy is required to achieve the benefits seen in clinical trials.[4]
- Cease statin therapy if liver enzymes are persistently elevated >3 times upper limit of normal (ULN), or creatine kinase (CK) is >5 times the ULN or if the patient complains of muscle pain and the CK is > 4 times ULN.[1]
- Use statins with caution in higher doses and in patients with renal failure as these can increase the risk of myotoxicity which may progress to rhabdomyolysis. [1]
- Use the combination of a statin with a fibrate or nicotinic acid (or cyclosporin) only on the advice of a specialist as this combination increases the risk of myotoxicity which may progress to rhabdomyolysis. [4]
- Older age (≥ 70 years), female gender, and low body weight are some factors that increase the risk of muscle disorders with statins. [27]
- Advise patients taking lipid-modifying drugs to promptly report any muscle pain, tenderness or weakness especially if accompanied by malaise or fever. [1]
- Atorvastatin and fluvastatin are the statins that are least affected by alterations in renal function. Reduce the dose of pravastatin and simvastatin by 50% if the estimated creatinine clearance (Cl_{Cr}) is < 60mL/min and < 30mL/min respectively. [28]
- Pravastatin and atorvastatin are less likely than the other statins to interact with warfarin therapy. Other statins may increase the INR and risk of bleeding. [5]
- Drug interactions which result in an increase in the plasma concentration of a statin, increase the potential for adverse effects especially myopathy and rhabdomyolysis.
- Pravastatin has a lower propensity to interact with patient's other medications (or grapefruit juice) than the other statins as it is not metabolized via the cytochrome P450 system (CYP3A4 and CYP2C9).
- Plasma levels of atorvastatin and simvastatin may increase with concomitant drugs that inhibit CYP3A4 hepatic or gut metabolism (e.g. macrolide antibiotics, azole antifungals, SSRIs, calcium channel blockers, protease inhibitors, cyclosporin and grapefruit juice).

- Fluvastatin is metabolized via the CYP2C9 isoenzyme, therefore, clinically significant drug interactions may occur between fluvastatin and CYP2C9 inducers (e.g. phenytoin) and CYP2C9 inhibitors (e.g. fluvoxamine, ritonavir). *(This drug interaction list is not exclusive-refer to individual product information).*
- Ezetimibe is the first member of a new class of drugs and has been used in only a limited number of patients in short term clinical trials where it has shown that it reduces LDL concentrations and is well tolerated. Use in a broader patient population is needed to provide further information about the safety profile of ezetimibe and it should not be used in preference to other agents that have safety data to support their use. [1]
- Be aware of clinically significant drug interactions between fibrates and statins, warfarin, anti-diabetic drugs and drugs that reduce renal function. [6]
- Drug (or diet) therapy for lipid lowering is inappropriate in pregnancy except if there is massive triglyceridaemia. [17] Ensure women of child bearing potential are taking adequate contraceptive precautions if such therapy is warranted.

7. Assisting prescribers to identify 'Quality Prescribing' questions

Decision-making steps

Step 1: What are the core principles of Quality Prescribing?
Is current prescribing judicious, appropriate, safe and effective?

Step 2: What are the related Quality Prescribing questions?

Step 3: What are the related data questions?
How do we measure and assess current usage against the Quality Prescribing questions?

Table 3: Putting decision-making steps into practice

Quality Prescribing principles	Quality Prescribing questions	Data questions
Is current prescribing judicious?	▪ Is the absolute risk of a CHD event assessed for each patient before the use of lipid-modifying drugs is considered?	▪ Proportion of patients taking lipid-modifying drugs who have their high absolute risk of a CHD event recorded.
	▪ Are lipid-modifying drugs prescribed for patients who are *not* at higher absolute risk of a CHD event?	▪ Proportion of lipid-modifying drug usage which is for patients who are *not* at higher absolute risk of a CHD event.
	▪ In patients at higher absolute risk of CHD, is a 6 week trial of dietary modification used prior to commencing lipid-modifying drugs?	▪ Proportion of patients taking lipid-modifying drugs and at a higher absolute risk of CHD, who did *not* have a 6 week trial of diet modification prior to drug therapy.
Is current prescribing appropriate?	▪ Are patients who have a history of MI or angina and total cholesterol > 3.5 mmol/L, prescribed lipid-modifying drugs?	▪ Indicator 13*: Percentage of patients with a history of MI who have NOT been prescribed a beta blocker, antiplatelet agent (or anticoagulant) and statin. #
Is current prescribing safe and effective?	▪ Is the effectiveness of lipid-modifying drugs monitored appropriately?	▪ Proportion of patients on lipid-modifying drugs whose lipid levels have *not* been measured in the last 12 months. ▪ Proportion of patients on lipid-modifying therapy whose lipid profile has *not* improved since commencing lipid-modifying therapy (diet or drug therapy). ▪ Proportion of patients on lipid-modifying therapy whose lipid levels have been measured in the last 12 months AND total cholesterol is *not* < 3.5 mmol/L.
	▪ Is the safety of lipid-modifying drugs monitored appropriately?	▪ Proportion of patients on lipid-modifying drugs who have *not* had liver and renal (statins and fibrates) function tests performed in the last 12 months.
	▪ Is the minimum effective dose prescribed?	▪ Proportion of patients prescribed statins who are using the maximum approved dose (should be less than 100%).

* National Prescribing Service. Indicators of quality prescribing in Australian general practice. March 2006

Patients with CHD could be identified by the recording of MI or angina in their past history or clinical condition. An alternative method is to identify them via drug therapy e.g. low dose aspirin or nitrate therapy.

8. Limitations of PBS data as a data source to review lipid-modifying drug prescribing

- Most PBS-listed lipid-modifying drugs are above general patient co-payment. Items below patient co-payment include fluvastatin 20 mg, pravastatin 10 mg, simvastatin 5 mg and fenofibrate 48 and 67 mg. The PBS dataset is, therefore, a largely accurate measure of the volume of lipid-modifying drug usage on the PBS.
- Knowledge of drug prices relative to the level of co-payment over time is required to interpret the PBS dataset. If the level of co-payment is increased, drugs for general patients that were previously captured by the PBS dataset, may fall below the level of co-payment and, therefore, no longer be captured for general patients. Drugs which were above the general patient co-payment before and are now under the co-payment include fenofibrate 67 mg (since January '05), fluvastatin 20 mg and simvastatin 5 mg (since August '05), and pravastatin 10 mg (since July '06).
- There may be some prescribing of lipid-modifying drugs as private prescriptions for patients who do not meet the PBS criteria for subsidy. This usage will not be captured by the PBS dataset. However, with the new PBS-eligibility criteria effective from 1 October 2006 more people will meet the PBS criteria for subsidy (people with a family history of cardiovascular disease, people with complications of diabetes and patients who already have cardiovascular disease).[26]
- Nicotinic acid was last listed on the PBS in August 2005.
- The PBS dataset can not identify the appropriateness of the prescribing of lipid-modifying drugs i.e. whether lipid-modifying drugs are being used in appropriate patients, if appropriate monitoring is performed and whether target lipid levels are achieved.
- Patients may purchase nicotinic acid and complementary therapies for dyslipidaemia such as fish oils (EPA, DHA) and plant sterols from community pharmacies. As these therapies are not listed on the PBS, their usage will not be captured by the PBS dataset.

9. Future developments

- **New drugs**

  - Rosuvastatin (Crestor) 5, 10, 20 and 40 mg. This new statin has Pharmaceutical Benefits Advisory Committee's (PBAC) positive recommendation and will be listed on the PBS. It is to be used as an adjunct to diet when the response to diet and exercise is inadequate for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia).
    http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-pbacrecjul06-positive
    Accessed September 2006

  - Amlodipine with atorvastatin (Caduet) 5 / 10 mg, 10 / 10 mg, 5 / 20 mg, 10 / 20 mg, 5 / 40 mg, 10 / 40 mg, 5 / 80 mg, and 10 / 80 mg. This new combination product has PBAC's positive recommendation and will be listed on the PBS. Indications for usage are to lower lipid levels and treat hypertension and/or angina.
    http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-pbacrecjul06-positive
    Accessed September 2006

  - Pitavastatin (previously known as itavastatin, itabavastin, nisvastatin) is a statin that induces a protective action in the vascular endothelial cell through the production of nitrous oxide. It has been available in Japan since 2003. The time line for marketing approval in Australia is not known.

10. References

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Appendix
Pharmaceutical Benefits Pricing Authority. Therapeutic Relativity Sheets.

Relativity Sheets show specific relativities and pricing comparisons between drugs within a therapeutic group. The relativities are usually based on PBAC advice but may also be historically based. Available at http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pricing-therelativity.htm). Last accessed September 2006

PHARMACEUTICAL BENEFITS PRICING AUTHORITY

Therapeutic Relativity Sheets

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1. Cholestyramine sachets and colestipol sachets have historically been priced the same on a per-sachet basis.

2. The PBAC has agreed to the listing of simvastatin with a 10% premium over cholestyramine at a dosage comparison of 13mg simvastatin versus 3 sachets of cholestyramine.

3. Pravastatin sodium has been recommended for listing on the basis of clinical equivalence to simvastatin on a mg to mg basis. PBAC was agreeable to comparison of the two drugs on an average daily dosage basis.

4. Fluvastatin sodium was recommended for listing with the advice that pricing be based on the drug's ability to reduce LDL cholesterol compared to simvastatin (approximately 22% for fluvastatin 20mg compared to 30% for simvastatin 10mg and approximately 25% for fluvastatin 40mg compared to 40% for simvastatin 20mg).

5. Fenofibrate was recommended for listing on a cost minimisation basis versus gemfibrozil with 160 mg fenofibrate (tablet formulation) = 1.2 g gemfibrozil.

6. Ezetimibe tablet 10 mg, for use in patients unable to take a statin, was recommended for listing on the basis of cost minimisation versus cholestyramine (10 mg daily = 17.2 g daily). For use as add-on therapy to a statin, the drug was recommended on the basis of acceptable cost effectiveness compared with placebo. The agreed price was based on 50% use for each of the two indications.

7. Atorvastatin was initially recommended for listing on the basis of cost minimisation, with the equieffective doses being 10mg atorvastatin = 20mg simvastatin. Subsequently, the drug was included in the HMG CoA reductase inhibitor therapeutic group and pricing has been reviewed on a weighted average monthly treatment cost basis. In July 2005, following the presentation of further data, the PBAC advised that:

- Atorvastatin is more effective than simvastatin in lowering LDL-cholesterol (LDL-C).
- The relative price differential modelled in the current submission's cost effectiveness analysis is acceptable.
- Any further price change in simvastatin should not result in any increase in this price relativity.
- The only basis for judging whether the price relativity could be further increased would be an incremental cost effectiveness analysis based on major cardiovascular events measured directly in randomised trials rather than based on predictions modelled from surrogate outcomes.

In line with the PBAC's advice in July and November 2005, atorvastatin has been removed from both the statin WAMTC and TGP groups. However, its pricing remains linked to that of simvastatin.

8. Ezetimibe with simvastatin (Vytorin®) was recommended on a cost-minimisation basis compared to the sum of the corresponding strengths of the individual components in patients with coronary heart disease, patients with diabetes mellitus and patients with homozygous familial hypercholesterolemia. The price for the simvastatin component of the combination tablet will be maintained at the same price as that of simvastatin.

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