National Prescribing Service Limited

Drug Utilisation Briefing

for

Enhanced Divisional Quality Use of Medicines Program

October 2002

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

Contents

Suggested citation for this document:

National Prescribing Service. Drug utilisation briefing for enhanced divisional quality use of medicines program: lipid-modifying drugs. October 2002.

The information contained in this material is derived from a critical analysis of a wide range of authorative evidence.
Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each patient.

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1. Clinical practice guidelines

- National Heart Foundation of Australia / The Cardiac Society of Australia and New Zealand. Lipid management guidelines-2001. Available from http://www.heartfoundation.com.au/index.cfm?page=40
- Australian Medicines Handbook 2002.
- *Summaries provided in NPS resources (see below)*

2. NPS resources available

(primarily via the NPS website at www.nps.org.au .Print copies available on request)

- NPS News 20 (February 2002).
- Prescribing Practice Review- PPR 17 (February 2002) *includes NZ Cardiovascular risk calculator.*
- PBS prescribing data feedback (circulated with PPR 17).
- *Management of Dyslipidaemia Program background material.
- *Practice Visits Program detailing card (June 2002) – *contains summary of guidelines & comparative information on lipid-modifying drugs.*
- Clinical audit pack (2002).
- Case studies x3.
    - CS 19 including summary of GP responses and expert commentary (2002).
    - * DCS 26 & 27 for small group case meetings with discussion points for facilitators.
- Using prescribing software to review your prescribing of lipid-modifying drugs: Instructions for Locum 3, Genie, Medical Director and Medical Spectrum software including points for prescribing review.
- Patient education material: "Prescription" for improving diet and lifestyle-pads.
- Heart Protection Study in perspective (August 2002) + further information for GPs (+ *further information for NPS facilitators).
- *Estimating coronary heart disease risk and the PBS criteria for subsidy of lipid-modifying therapy (June 2002).

**Only available to Divisions with NPS facilitators for use within their NPS Program, and therefore not available via the NPS website.*

3. What's what: lipid-modifying drugs

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, 40mg	Lescol®, Vastin®,	8023G, 8024H
	pravastatin	10, 20, 40 mg	Pravachol®	2833D, 2834E, 8197K
	simvastatin	5, 10, 20, 40, 80mg	Lipex®, Zocor®	2013Y, 2011W, 2012X, 8173E, 8313M
Fibrates	gemfibrozil	600mg	Ausgem®, Gemhexal®, Gemfibrozil-BC®, Jezil®, Lipazil®, Lopid®	1453L
Bile acid sequestrants	cholestyramine	4g, 8g cholestyramine	Questran Liter®	2967E, 2978R,
	colestipol	5g	Colestid®	1224K
Nicotinic acid	nicotinic acid	250mg	Available as generic only	1687T

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/pbs/general/schedule.htm

Complementary therapies for dyslipidaemia	Fish oils (EPA, DHA)	Most products contain 300mg EPA plus DHA / capsule		Not available on the PBS
	Plant sterols and stanols			
	Policosanol			

4. Definitions used in this document

Lipid-modifying drugs = HMG-CoA reductase inhibitors ('statins'), fibrates (gemfibrozil), bile acid sequestrants (cholestyramine and colestipol) and nicotinic acid.

Higher absolute risk of coronary heart disease =

As defined in table 1 of the National Heart Foundation of Australia / The Cardiac Society of Australia and New Zealand. Lipid management guidelines-2001 (available from http://www.heartfoundation.com.au/index.cfm?page=40

Known coronary heart disease (CHD) = history of myocardial infarction or angina.

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

The new Australian Lipid Management Guidelines:[1]

state

- there is strong evidence that lipid-modifying treatment reduces CHD progression, morbidity and mortality for people at high risk of CHD events;
- that treating those at highest absolute risk to lower plasma lipid levels has been shown to be cost effective;
- but, despite the potential for significant health gains, information from overseas and Australia shows that effective lipid-modifying therapy (lifestyle and drug therapy) is significantly underused in patients at higher absolute risk.

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.

Lipid-modifying therapy has greatest benefits for those at greatest absolute risk of CHD

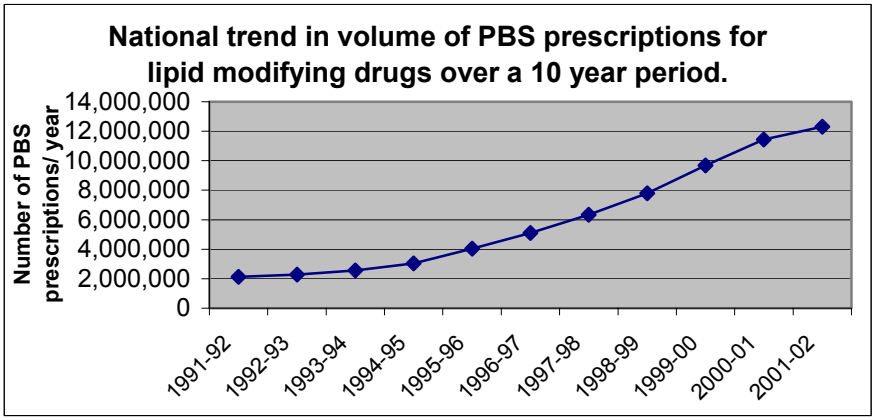
- In the 4S, CARE, and LIPID trials, patients with CHD had their absolute risk of CHD death or non-fatal MI reduced by up to 9% over five years by *simvastatin or pravastatin* over a wide range of plasma-cholesterol concentrations (4–8 mmol/L). A similar but less conclusive trend was achieved with gemfibrozil. To date there have been no outcome studies with atorvastatin or fluvastatin.[2]

- The issue of primary prevention therapy in individuals without CHD is less straightforward. The evidence from the principal primary prevention trials—WOSCOPS, AFCAPS/TexCAPS, and the Helsinki Heart Study —is not as persuasive as that from the secondary prevention trials.[2] These trials have not shown any difference in overall mortality between those taking lipid-modifying drugs and those who were not,[2] although *pravastatin* therapy was shown to reduce coronary mortality in men at high risk of CHD (e.g. angina but no previous MI) with LDL > 4.5 mmol/L.[3]

- Study results indicate that approximately 3 times as many people without CHD need to be treated for five years to prevent one CHD event than people with CHD.[2]

Usage of lipid-modifying drugs has increased significantly over the last decade but is it being targeted appropriately and used optimally?

- Lipid disorder was the fifth most frequently managed problem (2.9 per 100 encounters) in the BEACH survey of General Practice Activity in Australia 2000/01. The management of lipid disorder as a new problem accounted for only 0.7 per 100 encounters. Cholesterol and triglyceride reducers accounted for 2.6% of prescriptions and 2.4 per 100 encounters.[4]
- The usage of lipid-modifying drugs on the PBS has increased from just over 2 million prescriptions per year in 1991/2 to over 12 million prescriptions per year in 2001/2.[5]
- There has been a 27% increase in PBS volume of lipid-modifying drugs over the last two years.[6,7]



- Unfortunately 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 the appropriate patient group, or when they are used, if the appropriate monitoring is performed and whether target lipid levels are achieved.
- A recent Australian study concluded that the prescribing of lipid-lowering therapy for secondary prevention is suboptimal.[8] The study participants were 352 patients admitted to hospital with acute myocardial infarction or unstable angina (i.e. secondary prevention patients).
    - total serum cholesterol levels exceeded 5.5 mmol/L in 25% of the study patients who had been taking lipid-modifying therapy at time of hospital admission (N.B. Lower target of 4 mmol/L now advised);
    - 18% of patients with a total serum cholesterol >5.5 mmol/L and 34% of patients whose serum cholesterol was > 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 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 therapy are a concern

- Results in clinical trials were achieved with high levels of compliance with lipid-modifying therapy. However, an Australian study reported that 30% of patients prescribed lipid-modifying drug therapy stopped 6-7 months after starting and up to 60% had discontinued treatment within one year.[9,10] The authors conclude that this high apparent discontinuation rate with lipid-lowering drugs suggest significant wastage of resources in treatments that are initiated but not continued and a lost opportunity for heart disease prevention.

6. Principles of quality prescribing – lipid-modifying drugs

Judicious selection of management options

- Lipid-modifying drugs should not be prescribed to patients who do *not* have a higher absolute risk of CHD as defined by the NHFA/CSANZ lipid management guidelines 2001.[1]
- Manage other modifiable cardiovascular risk factors in all patients at higher absolute risk of CHD (e.g. stop smoking, reduce body weight, increase physical activity, reduce blood pressure towards target level, diabetes well controlled).[1,2]
- Treat secondary causes of dyslipidaemia, eg obesity, diabetes, hypothyroidism, obstructive liver disease, nephrotic syndrome, excess alcohol intake).[2]
- In all patients, the use of lipid-modifying drugs should be associated with dietary and lifestyle measures.[1,2]

Appropriate choice of medicines, where a medicine is considered necessary

The National Heart Foundation of Australia/ Cardiac Society of Australia and New Zealand. Lipid Management Guidelines -2001 should be referred to for recommendations on the appropriate use of lipid-modifying therapy including drug therapy.

- Lipid-modifying drugs should be used, in conjunction with diet therapy, in people with known CHD (a history of myocardial infarction or angina), who have a total cholesterol level above 4.0 mmol/L.[1,2]
- Lipid-modifying drugs should be considered for people at higher absolute risk of CHD whose lipid levels have remained above target levels (total cholesterol > 4.0 mmol/L) after a 6 week trial of dietary therapy.[1] *Eligibility for subsidy of lipid-modifying drugs will depend on meting the PBS criteria for subsidy.*[1,3]
- A statin is the drug of choice if hypercholesterolaemia is predominant.[1,2]
- Gemfibrozil is the drug of choice if hypertriglyceridaemia is predominant.[1,2]
- Combination drug therapy may be required 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.[2]
- The minimum effective dose should be prescribed. This is because the optimum dose for statins is uncertain[1], however, more than 80% of the reduction in LDL-cholesterol is achieved with 50% of the maximum dose,[2] and the risk of hepatotoxicity and myotoxicity increases as the dose of statin increases.[2] (Maximum doses: simvastatin 80mg daily, pravastatin 40mg daily, fluvastatin 40mg daily, atorvastatin 80mg daily).
- 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.[2]
- 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]
    - Total cholesterol <4.0 mmol/L LDL-cholesterol <2.5 mmol/L
    - HDL-cholesterol >1.0 mmol/L Triglycerides <2.0 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.[1]

- 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.[2]
- 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.[2]
- Use the combination of a statin with a fibrate (gemfibrozil) only on the advice of a specialist as this combination increases the risk of myotoxicity which may progress to rhabdomyolysis.[1]
- Patients taking lipid-modifying drugs should be advised to promptly report any muscle pain, tenderness or weakness especially if accompanied by malaise or fever.[4]
- Atorvastatin and fluvastatin are the statins that are least affected by alterations in renal function. Reduce the dose of pravastatin by 50% if the estimated creatinine clearance (Cl_{Cr}) is < 60mL/min or reduce the dose of simvastatin by 50% if the estimated Cl_{Cr} is < 30mL/min.[6]
- Pravastatin and atorvastatin are less likely than other statins to interact with warfarin therapy. Other statins may increase the INR and risk of bleeding.[2]
- 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 other statins as it is not metabolized via the cytochrome P450 system (CYP3A4 and CYP2C9).
- Clinically significant drug interactions may occur between atorvastatin and simvastatin with CYP3A4 inhibitors (e.g. cyclosporin, macrolides, azole antifungals, calcium channel blockers 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). *(These drug interaction lists are not exclusive-refer to individual product information).*
- Be aware of clinically significant drug interactions between gemfibrozil and statins, warfarin, anti-diabetic drugs and drugs that reduce renal function.[2]
- Statins and gemfibrozil are contra-indicated in pregnancy.[2] Ensure women of child bearing potential are taking adequate contraceptive precautions if such therapy is warranted.
- There are no scored formulations of 'statin' drugs available. Therefore the splitting of such tablets is not appropriate, as they have not been formulated to be utilised in such a way. In addition, compliance with statin therapy is already known to be low,[4,5] and compliance with medication is known to decrease with increasing complexity of the medication regimen. Requesting a patient to split tablets may decrease this compliance further.

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 Data questions?

How do we measure and assess current usage against the Quality Prescribing questions?

Putting decision-making steps into practice

Quality prescribing principle	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?	▪ For patients taking lipid-modifying drugs, is there a record that the patient is at higher absolute risk of a CHD event?
	▪ 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.
	▪ Have all patients on lipid modifying drugs been educated about diet / lifestyle measures.	▪ Proportion of patients taking lipid-modifying drugs who have *not* been given dietary / lifestyle advice
	▪ In patients at higher absolute risk of CHD, is a 6 week trial of dietary modification used prior to commencing lipid-modifying drugs? (patients with known CHD should have dietary advice but may start drug therapy at the same time).	▪ Proportion of patients at higher absolute risk of CHD taking lipid-modifying drugs, 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 > 4mmol/L, prescribed lipid-modifying drugs?	▪ Proportion of patients with a history of MI or angina and a total cholesterol > 4mmol/L who are prescribed lipid-modifying drugs.#
	▪ Are patients at higher absolute risk of CHD prescribed lipid-modifying drugs (if a 6 week trial of dietary modification has failed to reduce cholesterol to < 4mmol/L)?	▪ Proportion of patients in identifiable high risk groups (e.g. diabetics) with lipid levels outside target levels despite dietary modification, who are prescribed lipid-modifying drugs.

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 drugs whose lipid levels have been measured in the last 12 months AND total cholesterol is *not* < 4mmol/L.
	▪ Is the safety of lipid-modifying drugs monitored appropriately?	▪ Proportion of patients using statins or gemfibrozil who have *not* had a liver function test 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%).

***Data questions:** *This 'step' is for further development by the Data consultancy in consultation with NPS but initial questions are included here as examples. The accessibility, interpretation and limitations of obtaining data to answer these questions all require further investigation.*

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

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

- All lipid-modifying drugs (with the exception of nicotinic acid) are above patient co-payment therefore the PBS dataset is an accurate measure of the volume of lipid-modifying drug usage on the PBS.
- However the PBS dataset can not identify the appropriateness of the prescribing of lipid-modifying drugs - i.e. whether lipid-modifying drug therapy is being used in the appropriate patient group or when it is used whether target lipid levels are achieved and if the appropriate monitoring is performed.
- 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.
- Patients may purchase complementary therapies for dyslipidaemia, such as fish oils (EPA, DHA), plant sterols and policosanol, 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
  - Several new statins are at various stages of drug development but no published clinical trials are available at present although some results have been published in abstract form.
  - Several other new agents that reduce LDL cholesterol by affecting different steps in cholesterol and lipoprotein synthesis are also in various stages of development.
    - The first drug in this group, ezetimibe (Zetia®), was approved by the American FDA in October 2002 as monotherapy and for use alongside any of the currently marketed statins. Ezetimibe works by preventing the intestinal absorption of cholesterol, whereas statins inhibit the liver's natural production of cholesterol. Clinical trials have shown that ezetimibe, when given to patients already taking a statin, can reduce levels of LDL cholesterol by 25% more than the statin alone. The manufacturers (Schering-Plough and Merck) have said that they are on track by "late 2003" to seek US approval for a pill containing both ezetimibe and simvastatin (Zocor®).
  - The time line for marketing approval for any of these agents in Australia is not known.
- Potential changes in clinical practice guidelines
  - No information available.

10. Indicators of quality prescribing under development by the NPS

To follow- will include a link to an indication for therapy.

11. Potential changes in prescribing if principles of quality prescribing outlined above are followed

To follow.

12. Cost comparison for lipid-modifying drug therapies and pharmacoeconomic considerations

To follow.

13. References

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

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Principles of quality prescribing – lipid-modifying drugs

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Appendix 1
Pharmaceutical Benefits Pricing Authority. Therapeutic Relativity Sheets.

(available on line at http://www.health.gov.au/pbs/pricing/therelativity.pdf)

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.

PHARMACEUTICAL BENEFITS PRICING AUTHORITY

Therapeutic Relativity Sheets

ATC C10 – SERUMLIPIDREDUCING AGENTS	**Effective Date:** 12/98	PAGE **1** OF **1**

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 vs. 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. Atorvastatin was accepted for listing on the basis of cost minimisation, 10mg atorvastatin compared to 20mg simvastatin.
6. *Cerivastatin was recommended for listing on the basis of superiority to fluvastatin but inferiority compared to simvastatin in its ability to lower LDL cholesterol. Pricing is based on the daily cost per 10% lowering of LDL cholesterol. [Approximate reduction in LDL cholesterol: simvastatin 10 mg = 30%, 20 mg = 40%; cerivastatin 200 mg = 25.8%, 300 mg = 29.2%.]*