Reclassification of simvastatin to pharmacy only

Submission to Medicines Classification Committee

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1.1.1 Part A

1. *International Non-propriety Name (or British Approved Name or US Adopted Name) of the medicine*

Simvastatin.

2. *Proprietary name(s)*

To be advised.

3. *Name of company/organisation/individual requesting reclassification*

HeartCare Plus Ltd.

4. *Dose form(s) and strength(s) for which a change is sought*

Tablet. Simvastatin 10mg

5. *Pack size and other qualifications*

Blister packed for 30-day supply.

6. *Indications for which change is sought*

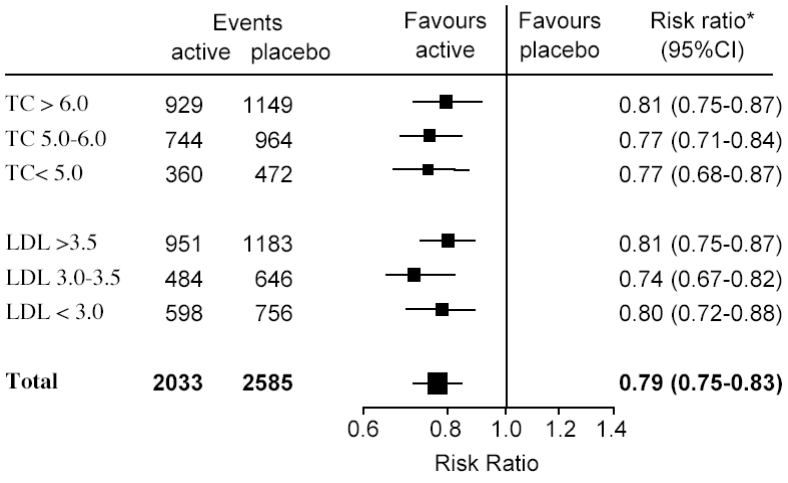
For patients with an absolute risk of a cardiovascular event of 10-15% over the next 5 years (and total cholesterol between 4-8 mmol/l) to reduce the risk of cardiovascular disease. It is to be used concurrently with diet and lifestyle changes.

The over-the-counter product will therefore be targeted to men aged over 45 years and women aged over 55 years (the population recommended for screening [1]) who are at risk of cardiovascular disease (calculated using absolute risk charts which are widely available and in use in New Zealand, see page xxii of reference [2]) but without existing disease. This indication for the over-the-counter product excludes individuals with existing or previous cardiovascular disease (whose risk is over 20%) or significantly raised cholesterol (above 8mmol/l), as they require referral to and management by a general practitioner. [1]

For New Zealanders screened according to the recent New Zealand Guidelines Group (NZGG) guideline *The assessment and management of cardiovascular risk* [1] (supplied) and found to be at 10-15% risk of a cardiovascular event the benefits of low dose simvastatin would be substantially greater than their side effects. However, the relative cost benefit analysis of widespread treatment of this moderate-to-high risk population (approximately 125,000 persons) with current strategies (involving general practitioner time, monitoring, prescription costs and current drug costs) concluded the costs were too high to recommend prescription-based treatment in the guideline. Note that while this group is labelled as “moderate” risk, in many other disease conditions a 1 in 10 chance of a fatal or life-threatening event would be considered “high”.

This approach is consistent with the NZGG cardiovascular risk guideline [1], that treatment should be based on absolute risk not single risk factor levels. Landmark trials, such as the Heart Protection Study (HPS) definitively show that statins should be provided largely irrespective of baseline cholesterol levels to individuals at moderate to high cardiovascular risk (see Figure). [3, 4] The HPS, LIPID [5] and other major trials also show that the benefits of statin therapy extend to all major

Reduction of CV events with statin cholesterol lowering in Heart Protection Study, by baseline cholesterol

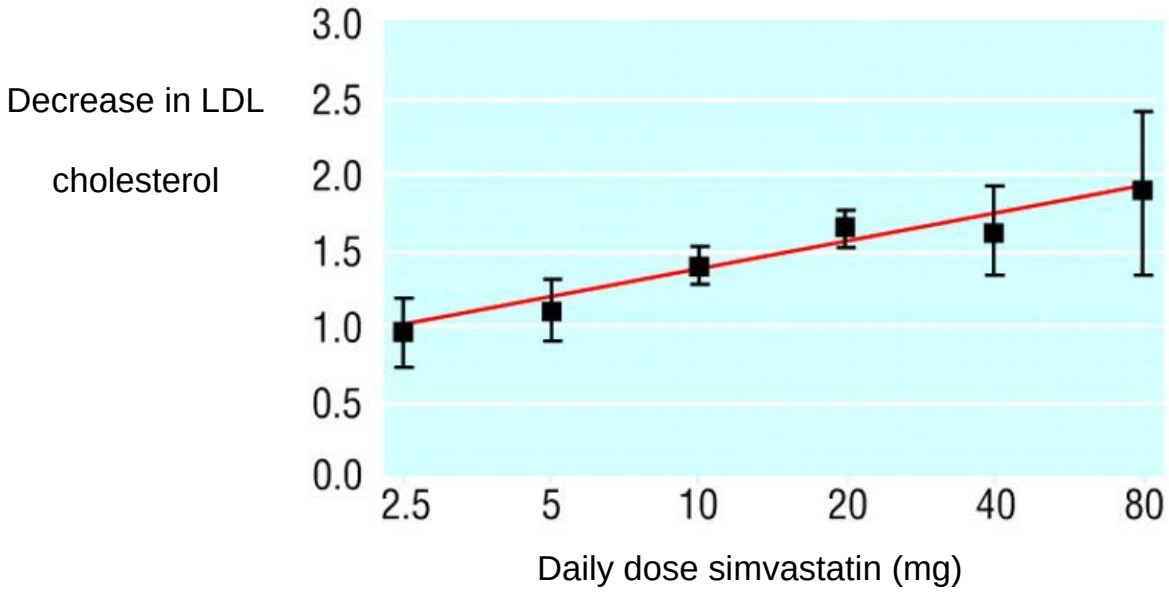


subgroups regardless of age, sex, and presence of other cardiovascular medications (e.g. blood pressure lowering medication, antiplatelet agents).

The over-the-counter product will be targeted to individuals at moderate risk at a dose of 10mg daily. The currently approved dosage range for simvastatin is 5-80mg per day as a single dose in the evening. In those at high risk of coronary heart disease or with existing disease the starting dose is 40mg daily, for hyperlipidaemia alone it is 20mg. [6] Due to the relatively flat dose-response curve of statins the majority of the effect is achieved at low dose, such that at 10mg treatment with simvastatin results in reductions in LDL cholesterol that almost as great as those achieved with 40mg (see Figure). [4] A systematic review of all randomised trials of statins, clearly shows that their beneficial effects on cardiovascular events are all or virtually all explained by the extent of their efficacy in lowering cholesterol [4]). Hence, a 10mg dose can be expected to achieve substantial reductions in cholesterol and hence in cardiovascular events of almost as large a magnitude as that seen in clinical trials of larger doses.

Dose response effects of simvastatin:

meta-analysis of all randomised trials



A 10mg dose would minimise the risk of serious adverse effects in light of increased access. This rationale is also the basis of an application for reclassification of Simvastatin in the UK [7].

7. *Present classification of medicine*

Prescription only.

8. *Classification sought*

Pharmacy only.

9. *Classification status in other countries (especially Australia, UK, USA, Canada)*

Prescription only medicine in Australia, UK, USA, Canada.

However, statins including simvastatin have recently been proposed as potential candidates for reclassification from prescription only medicine to pharmacy medicine in the UK. This follows a commitment by the National Health Service to introduce a wider range of over-the-counter medicines. A list of medicines that are potential candidates for reclassification was devised by Medicines and Healthcare Products Regulatory Agency (MHRA, previously the Medicines Control and Medical Devices Agencies) in the UK together with a working group of stakeholders. [8]

Consistent with this policy, Johnson & Johnson, MSD Consumer Pharmaceuticals submitted an application to reclassify ZOCOR® Heart-Pro tablets containing simvastatin 10mg from a prescription only medicine to pharmacy only. [7] The consultation period for this application finishes on 16 January 2004. HeartCare Plus will supply the Medicines Classification Committee with copies of the UK consultation and decision when they become available.

10. *Extent of usage in NZ and elsewhere (e.g. sales volumes) and dates of original consent to distribute*

Simvastatin was approved in New Zealand in December 1998. The UK reclassification application referred to above, estimated exposure to simvastatin at over 73 million patient-years of treatment. [7]

11. Labelling or draft labelling for the proposed new presentation(s)

To be advised.

12. Proposed warning statements if applicable

The package leaflet will contain information about contraindications, interactions, and adverse effects such as the rare risks of myopathy/rhabdomyolysis and liver function abnormalities. This will be based on the existing consumer medicine information (CMI) for simvastatin (see Appendix 1). The package insert will also include information about cardiovascular disease and absolute risk plus diet and lifestyle advice consistent with the NZGG cardiovascular risk management guideline. [1]

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change

Lipex (MSD) Simvastatin 10mg, 20mg, Zocor (MSD) Simvastatin 10mg, 20mg

Part 2

1. *A statement of the benefits to both the consumer and to the public expected from the proposed change*

Cardiovascular disease is the leading cause of death in New Zealand, accounting for 40% of all deaths, and is also the leading cause of loss of healthy life years. [1, 9] The Government has agreed to give priority to a limited number of health goals that include the reduction of cardiovascular heart disease.

While age-standardised mortality has halved over the past 30 years, the total number of deaths from cardiovascular disease has changed little because of the growing number of older people and at-risk individuals.

Cardiovascular disease is the main reason for the increasing difference in life expectancy between Māori and nonMāori. [9, 10] The burden of cardiovascular disease in Māori and lower socioeconomic groups falls disproportionately on those at a younger age. [1]

Cardiovascular disease can be reduced through lifestyle change and appropriate drug therapy. [1] Reducing the burden of cardiovascular disease and removing these inequalities will require a comprehensive integrated public health programme that includes screening for absolute cardiovascular disease risk and increasing access to statins.

Over-the-counter products are much more accessible for consumers by virtue of the ease of visiting pharmacies alone. Availability of statins directly via pharmacies will reduce barriers to access and potential for higher levels of use particularly in populations at increased risk, i.e. in areas of greater deprivation. There is potential to reduce health inequalities by targeting delivery of the over-the-counter product with subsidies, and promoting this initiative with, for example, specially trained Marae nurses (a similar approach was successfully trialed and implemented with nicotine replacement therapy) and primary health organisations. The applicants are in discussion with the National Heart Foundation, Te Hotu Manawa Māori and the Ministry of Health to facilitate mechanisms for such improved access. This approach will have benefits for the individuals involved, will reduce overall the nation's cardiovascular toll, and could address inequalities in health status as part of a larger integrated comprehensive public health programme.

The economic analysis accompanying the NZGG cardiovascular risk guideline found that screening of adults for cardiovascular disease and treating all those over 10% 5-year risk with statins had cost-effectiveness ratios very favourable in comparison to other widely used interventions. However concern was raised about the extra resources required for statin subsidies and general practitioner caseloads if the threshold is set at 10% rather than 15%, since this group numbers over 100,000. [1] This factor may have contributed to the guideline advocating pharmacological treatment of those over 15% and "specific individualised lifestyle advice" for the 10-15% group. A low-cost over-the-counter product manufactured by a generics company would solve many of these problems.

2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

Pharmacies will be provided with training to ensure appropriate use of this medicine and protocols for referral of individuals to their general practitioners as indicated. The training will include the development of an information pack containing the NZGG cardiovascular risk guideline steps to cardiovascular risk assessment [1] (see Appendix 2). In order to calculate risk consumers will be required to have blood pressure and cholesterol measurements performed. It is planned to develop a protocol for pharmacies and a training proposal in conjunction with the National Heart Foundation, Pharmacy Guild and Pharmacy Society, and primary care. These will address identification of the consumer for whom this product will be suitable and also those who may be at higher risk and should be referred to their general practitioner.

It is anticipated that the training will:

- Provide information on the major causes of cardiovascular disease.
- Provide information on absolute risk assessment and guidelines for referral to a general practitioner.
- Provide information on the mode of action, contraindications and precautions for use and possible adverse effects of simvastatin.
- Review other interventions to reduce the risk of cardiovascular disease, including specific advice about smoking cessation, diet, weight loss and exercise.
- Include advice for individuals making repeat purchases including the reinforcing of safety messages, follow-up and indications for referral to a general practitioner.

3. *Relevant comparative data for like compounds*

The reader is referred to the paper by Law et al: Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis (supplied). [4]

4. *Local data or special considerations relating to NZ*

Cardiovascular disease is the leading cause of death in New Zealand. A recent Ministry of Health report on the Burden of Disease from nutrition estimated a very high burden from high blood cholesterol in New Zealand, with over 4,500 deaths annually. [11] This burden from cholesterol is considerably greater than that seen in other countries such as the UK, Australia and USA, reflecting our relatively high heart disease rates, in large part as a result of many decades of high cholesterol levels.

New Zealand has historically had relatively poor access to statins compared to other developed countries. This situation is considered to be a key factor contributing to the continued high toll from cardiovascular disease. [12, 13] Increasing the uptake of statins with an over-the-counter product would provide an important strategy to achieve the recommendations of screening and treatment by absolute risk in the NZGG cardiovascular risk guidelines. [1]

HeartCare Plus Ltd has approached the National Heart Foundation to collaborate to develop an innovative and cost-effective prevention programme to reduce cardiovascular disease in population groups most at risk. A key component of this initiative will be the approval of over-the-counter simvastatin to be available through an integrated community based health promotion programme. The programme's aim would be to significantly reduce the risk of heart disease in population groups most at risk, particularly Māori and Pacific peoples. It would achieve this goal by increasing the availability of statins alongside lifestyle changes.

5. *Interactions with other medicines*

The potential for interactions will be minimised with the 10mg dose.

Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other medicines metabolised by CYP3A4. Potent inhibitors of CYP3A4 (itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, cyclosporine) increase the risk of myopathy by reducing the elimination of simvastatin. The risk of myopathy is also increased by the following lipid-lowering medicines that are not potent inhibitors of CYP3A4, but which can cause myopathy when given alone: gemfibrozil, other fibrates (except fenofibrate), niacin (nicotinic acid) (≥1 g/day). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. [6]

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin. Patients on diltiazem treated concomitantly with simvastatin 80 mg have a slightly increased risk of myopathy. [6]

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of medicines metabolised by CYP3A4. The effect of typical consumption (one 250-ml glass daily) is minimal (13% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration-time curve) and of no clinical relevance. However, very large quantities (over 1 litre daily) significantly increase the plasma levels of HMG-CoA reductase inhibitory activity during simvastatin therapy and should be avoided. [6]

In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised Ratio, increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for

patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants. [6]

Concomitant administration of simvastatin and digoxin in normal volunteers resulted in a slight elevation (less than 0.3ng/ml) in medicine concentrations (as measured by a digoxin radioimmunoassay) in plasma compared to concomitant administration of placebo and digoxin. [6]

6. *Contraindications*

- Hypersensitivity to any component of the HeartCare Plus preparation.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing. [6]

7. *Possible resistance*

Not applicable.

8. *Adverse events - nature, frequency etc.*

Statins are remarkably safe and well tolerated.[3, 14, 15] Serious side effects are very rare (<1:100,000). [1] They have been used in tens of millions of people and have exceptionally well established safety profiles. In the controlled clinical studies fewer than 2 percent of patients were discontinued due to adverse effects attributable to simvastatin.[6] Only a few people in every 10,000 treated for 5 years with simvastatin suffer myopathy or markedly elevated liver enzymes and this appears to be dose-related. [3, 14] Fatal rhabdomyolysis is estimated to occur at a rate of 0.15 deaths per 1 million prescriptions. [16] The risk of myopathy/rhabdomyolysis is dose related and occurs in less than 0.1% in doses of 40mg per day and under. [6, 16] Cerivastatin, another of the statin class, was withdrawn in 2001 because of myotoxicity but it appears the risk with this medicine is 10 times higher than other statins. [17]

In the pre-marketing controlled clinical studies, adverse effects occurring with a frequency of 1 percent or more and considered by the investigator as possibly,

probably or definitely medicine-related were: abdominal pain, constipation and flatulence. Other adverse effects occurring in 0.5-0.9% of patients were asthenia and headache. [6]

Myopathy has been reported rarely. In HPS involving 20, 536 patients treated with 40mg/day of simvastatin (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with simvastatin and patients treated with placebo over the mean 5.3 years of the study. In this mega-trial, only serious adverse effects and discontinuations due to any adverse effects were recorded. Discontinuation rates due to adverse effects were comparable (4.8% in patients treated with simvastatin compared with 5.1% in patients treated with placebo). The incidence of myopathy was < 0.1% in patients treated with simvastatin. Elevated transaminases (>3X ULN confirmed by repeat test) occurred in 0.21% (n = 21) of patients treated with simvastatin compared with 0.09% (n = 9) of patients treated with placebo. [3] In 4S, involving 4444 patients treated with 20-40 mg/day of simvastatin (n=2221) or placebo (n=2223), the safety and tolerability profiles were comparable between treatment groups over the median 5.4 years of the study. [6]

Marked and persistent increases of serum transaminases have been reported infrequently. Elevated alkaline phosphatase and γ-glutamyl transpeptidase have been reported. Liver function test abnormalities have generally been mild and transient. [6]

The principal concerns of rare instances of myopathy and hepatic effects will be addressed both in the pharmacy protocol and the product labelling. This labelling will inform consumers to avoid medications that may interact with simvastatin, and to stop taking simvastatin and see their general practitioner if they develop unexplained generalised muscle pain, tenderness, weakness, or jaundice etc.

Monitoring

The simvastatin datasheet and the NZGG cardiovascular risk management guideline recommend liver function tests (LFT) are performed before treatment begins. [1, 6] The pharmacy protocol will require LFT testing at the time of obtaining the baseline cholesterol levels. Baseline creatinine kinase is not required. The protocol will also include a recommendation that if symptoms of liver or muscle problems develop the person is referred to their general practitioner. The value of additional monitoring of

creatinine kinase and LFTs is uncertain, in particular because it is not known whether monitoring would avoid events. [18]

9. Potential for abuse or misuse

The potential for abuse or misuse of this product is low. The pharmacy protocol and labelling will advise against taking the over-the-counter product if the consumer is already on prescribed lipid lowering therapy. A few cases of simvastatin overdose have been reported with 3.6g being the maximum dose taken. All patients recovered without sequelae. The datasheet recommends usual overdose treatment measures.[6]

Summary

The overall risk to benefit to the community of pharmacist availability of simvastatin is regarded as favourable. Simvastatin has a well-established safety profile and reclassification to Pharmacy only status does not raise any additional safety concerns. There is no need for further investigation of activity or side effects. Therefore, there is no direct or indirect danger to health when simvastatin is used without medical supervision but with the advice of a pharmacist. The pharmacy protocol will be consistent with the recent NZGG guideline on cardiovascular risk assessment and management and pharmacies will be supplied with a comprehensive pharmacy training package based on this guideline. Over-the-counter simvastatin has the potential to significantly reduce the burden of cardiovascular disease in New Zealand and reduce inequalities.

References

1. New Zealand Guidelines Group, et al., *Best practice evidence-based guideline. The assessment and management of cardiovascular risk.* 2003, New Zealand Guidelines Group,.
2. Jackson, R., *Updated New Zealand cardiovascular disease risk-benefit prediction guide.* BMJ, 2000. **320**: p. 709-710.
3. Heart Protection Study Collaborative Group, *MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial.* Lancet, 2002. **360**(9236): p. 7-22.
4. Law, M.R., N.J. Wald, and A.R. Rudnicka, *Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis.* BMJ, 2003. **326**: p. 1423-30.
5. Tonkin, A., et al., *Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels.* New England Journal of Medicine, 1998. **339**: p. 1349-1357.
6. Merck Sharp & Dohme (New Zealand) Limited, *LIPEX datasheet*. 2003, Medsafe.
7. Johnson & Johnson and MSD Consumer Pharmaceuticals, *Request to reclassify Zocor Heart-Pro from POM to P*. 2003, Medicines Healthcare Products Regulatory Agency,.
8. Medicines Healthcare Products Regulatory Agency, *Current consultative documents: Reclassification strategy: therapeutic categories*. 2002, Medicines Healthcare Products Regulatory Agency,.
9. Tobias, M. and NZ Burden of Disease Study team, *The burden of disease and injury in New Zealand.* www.moh.govt.nz Public Health Intelligence. Occasional Bulletin 1., 2001.

10. Ajwani, S., et al., *Decades of disparity: Ethnic mortality trends in New Zealand 1980-1999.* 2003, Ministry of Health and University of Otago: Wellington.
11. New Zealand Ministry of Health and University of Auckland, *Nutrition and the burden of disease: New Zealand 1997-2011*. 2003, Ministry of Health: Wellington.
12. Begg, E., et al., *The sorry saga of the statins in New Zealand - pharmacopolitics versus patient care.* New Zealand Medical Journal, 2003. **116**(1170).
13. Moodie, P., S. Metcalfe, and W. McNee, *Response from PHARMAC: difficult choices.* New Zealand Medical Journal, 2003. **116**.
14. Pfeffer, M.A., et al., *Safety and tolerability of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project.* Circulation, 2002. **105(20)**: p. 2341-6.
15. Hayden, M., et al., *Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the US Preventive Services Task Force.* Annals of Internal Medicine, 2002. **136**: p. 1661-72.
16. Thompson, P., P. Clarkson, and R. Karas, *Statin-associated myopathy.* Journal of the American Medical Association, 2003. **289**(13): p. 1681-90.
17. Lane, R. and M. Phillips, *Rhabdomyolysis. Has many causes, including statins, and may be fatal.* British Medical Journal, 2003. **327**: p. 115-6.
18. Wald, N. and M. Law, *A strategy to reduce cardiovascular disease by more than 80%.* British Medical Journal, 2003. **326**: p. 1419-1424.
19. Merck Sharp & Dohme (New Zealand) Limited, *Lipex consumer medicine information*. 2003, Medsafe.

Appendix 1

Warning labelling based on Lipex CMI [19]

Do not take simvastatin 10mg:

- If you have an allergy to simvastatin. Symptoms of an allergic reaction may include skin rash, itchiness, shortness of breath, swelling of the tongue or face, or painful joints. Tell your pharmacist if you have any allergies to any other medicines or any other substances, such as foods, preservatives or dyes.
- If you are pregnant, trying to get pregnant, suspect that you are pregnant or breast-feeding.
- If you have liver disease. If you have ever had liver problems you may need a blood test to make sure you have no active disease. Also tell your pharmacist if you drink alcohol regularly.
- If you have had muscle pain, tenderness or weakness from other medicines used to treat high cholesterol or triglycerides.

If you are not sure whether you should start taking simvastatin 10mg, talk to your pharmacist.

Because taking simvastatin 10mg with any of the following medicines can increase the risk of muscle problems, it is particularly important to tell your pharmacist if you are taking:

- gemfibrozil and bezafibrate, other lipid lowering medication.
- erythromycin and clarithromycin, antibiotics used to treat infections.
- ketoconazole and itraconazole, medicines used to treat certain fungal infections.
- cyclosporin, a medicine used to suppress the immune system.
- nefazodone, a medicine used to treat depression.
- amiodarone, a medicine used to treat an irregular heartbeat.
- verapamil or diltiazem, medicines used to treat high blood pressure, angina, or other heart conditions.

- indinavir, nelfinavir, ritonavir, saquinavir, medicines used to treat HIV infection.
- large doses (≥ 1g/day) of niacin or nicotinic acid.

It is also important to tell your pharmacist if you are taking coumarin anticoagulants (medicines used to prevent blood clots, e.g. warfarin). These medicines may be affected by simvastatin 10mg, or may affect how well it works. You may need different amounts of your medicine, or you may need to take different medicines.

Appendix 2

Assessment of cardiovascular risk [1]

Treatment decisions are based on the likelihood an individual will have a cardiovascular event over a given period of time. This replaces decision-making based on individual risk factor levels. By knowing the risk level an individual and their practitioner can make decisions for prevention and treatment of cardiovascular disease, including lifestyle advice, diabetes care, the prescription of lipid-modifying and blood pressure lowering medication and/or medication after myocardial infarction or ischaemic stroke.

The following steps explain the actions taken at each stage.

STEP 1: Select people for risk assessment

People with diabetes should have risk assessments from the time of diagnosis.

Mäori, Pacific peoples and people from the Indian subcontinent: screen men from age 35 years and women from age 45 years.

People with known cardiovascular risk factors or at high risk of developing diabetes: screen men from age 35 years and women from age 45 years.

Asymptomatic people, without known risk factors: screen men from age 45 years and women from age 55 years.

STEP 2: Measure and record risk factors

A comprehensive cardiovascular risk assessment includes measurement and recording of the following:

- age
- gender
- ethnicity
- smoking history
- a fasting lipid profile
- a fasting plasma glucose
- the average of two sitting blood pressures
- family history
- waist circumference
- body mass index.

STEP 3: Risk Assessment

5-year cardiovascular risk in the following groups is assumed clinically to be more than 20%:

• people who have had a previous cardiovascular event (angina, myocardial infarction, angioplasty, coronary artery bypass grafts, transient ischaemic attack, ischaemic stroke or peripheral vascular disease)

• people with some genetic lipid disorders (familial hypercholesterolaemia, familial defective ApoB and familial combined dyslipidaemia)

• people with diabetes and overt nephropathy or diabetes with other renal disease.

Cardiovascular risk in all other people can be calculated using the National Heart Foundation's cardiovascular risk tables or an electronic decision-support tool based on the Framingham risk equation for first cardiovascular events.

People with isolated elevated single risk factor levels will have at least greater than 15% cardiovascular risk over 5 years. They should have a risk assessment because, when all risk factors are taken into account, they may have a calculated 5-year cardiovascular risk higher than this. Isolated elevated single risk factor levels are defined as:

• Total cholesterol (TC) greater than 8 mmol/L

• TC:HDL cholesterol ratio greater than 8

• Blood pressure consistently greater than 170/100 mm Hg.

Supporting documents

1 New Zealand Guidelines Group, et al., *Best practice evidence-based guideline. The assessment and management of cardiovascular risk.* 2003, New Zealand Guidelines Group.

2 MHRA. Reclassification strategy: therapeutic categories potentially suitable for reclassification from POM to P.

3 Johnson & Johnson and MSD Consumer Pharmaceuticals, *Request to reclassify Zocor Heart-Pro from POM to P*. 2003, Medicines Healthcare Products Regulatory Agency.

4 Law, M.R., N.J. Wald, and A.R. Rudnicka, *Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis.* BMJ, 2003. **326**: p. 1423-30.

5 Merck Sharp & Dohme (New Zealand) Limited, *LIPEX datasheet*. 2003, Medsafe.

6 Merck Sharp & Dohme (New Zealand) Limited, *Lipex consumer medicine information*. 2003, Medsafe.

7 Wald, N. and M. Law, *A strategy to reduce cardiovascular disease by more than 80%.* British Medical Journal, 2003. **326**: p. 1419-1424.

8 Thompson, P., P. Clarkson, and R. Karas, *Statin-associated myopathy.* Journal of the American Medical Association, 2003. **289**(13): p. 1681-90.