Reclassification of Simvastatin

Present classification: **Prescription Medicine**

Sought classification: **Restricted Medicine**

Submission to: Medicines Classification Committee
Medsafe New Zealand

Submission from: GlaxoSmithKline
Consumer Healthcare

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Sponsor Information

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Glossary of Terms and Abbreviations

4S	Scandinavian Simvastatin Survival Study
AFCAPS / TexCAPS	Air Force / Texas Coronary Atherosclerosis Prevention Study
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CARE	Cholesterol and Recurrent Events
CHD	Coronary Heart Disease
CV	Cardiovascular
FDA	Food and Drug Administration
GSL	General Sales List
HPS	Heart Protection Study
LDL	Low Density Lipoprotein
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
NZ	New Zealand
RR	Relative Risk
UK	United Kingdom
US	United States
WOSCOPS	West of Scotland Coronary Prevention Study

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1 EXECUTIVE SUMMARY

This purpose of this Executive Summary is to summarise the evidence supporting a reclassification of simvastatin 10 mg from a Prescription Medicine to a Restricted Medicine in New Zealand. Simvastatin 10 mg is intended to reduce the risk of CHD by reducing cholesterol in individuals with a mild to moderate risk of the disease.

Public Health Benefits of Cholesterol Reduction

Coronary heart disease (CHD) is a major public health burden in New Zealand, with considerable epidemiological, financial and medical consequences. Coronary heart disease is also the leading cause of death in New Zealand, accounting for 40% of all deaths, with mortality rates highest in Māori and Pacific peoples.

The direct and in-direct medical costs of CHD place a heavy burden on the New Zealand health budget. For example, PHARMAC spent more than $ 50 million NZ on lipid modifying agents in the year ending in June 2004. In addition, fatal and non-fatal CHD accounted for approximately 30,000 annual public hospital admissions. In light of these high costs and flow-on impacts, even small reductions in the incidence of CHD would produce substantial savings to the New Zealand health budget.

Traditionally many initiatives on CHD reduction have focussed on patients at higher risk. Importantly, as a large number of New Zealand deaths attributed to CHD occur outside of hospital, in patients without a previous history of heart disease, treating only high-risk patients may limit the ability to reduce cardiovascular morbidity and mortality. To lessen the public health burden in

New Zealand, efforts to reduce the risk of CHD therefore need to extend beyond the treatment of high-risk patients.

Population studies have shown that it is possible to reduce the risk of CHD by lowering cholesterol. Numerous, well-controlled studies, with many thousands of patient-years research, have demonstrated the favourable benefit to risk profile of the statin group of drugs for lowering cholesterol and reducing the risk of CHD. Meta-analyses of individual patient data from prospective observational studies demonstrate the same general pattern of association between cholesterol levels and the relative risk of cardiovascular disease. For example, a 0.6mmol/L difference in total blood cholesterol corresponds to a 27% relative difference in coronary risk, and this association is consistent in the total cholesterol range between 4mmol/L to 9mmol/L. Furthermore, there does not appear to be a threshold under which a reduction in cholesterol is not associated with a reduction in the risk of CHD.

Fundamental to the determination of an individual's absolute cardiovascular risk is the synergistic effect of all risk factors. In individuals with the same cholesterol levels, the absolute risk can vary more than 20 fold. A review by researchers from the University of Auckland, which was recently published in The Lancet highlights that single risk factors such as blood pressure and cholesterol may have a minor effect on a patient's absolute risk in the absence of other risk factors, but they can have a major effect in the presence of several risk factors [Jackson R. et al., 2005].

Efficacy & Safety of low dose Simvastatin

The group of drugs known as the statins are established as being the cornerstone of lipid lowering pharmacotherapy, with simvastatin being arguably the best characterised and most widely used.

Rational extrapolation from well-controlled studies supports the safe and effective use of low dose simvastatin in the proposed target population (5-15% absolute risk of cardiovascular event in 5 years). In this regard, a recent meta-analysis, based on 164 randomised, placebo-controlled clinical trials on statins, has shown that 10 mg of simvastatin can deliver a 27% reduction in low density lipoprotein cholesterol and a 33% reduction in the risk of an ischaemic heart disease event after three to five years of treatment.

In terms of safety, the statins as a group are generally very well tolerated. The incidence of serious adverse events such as hepatotoxicity and myotoxicity are low, with the incidence rates comparable between statin and placebo groups in large, controlled clinical trials.

The overall efficacy and risk benefit profile of simvastatin show that populations who receive this drug and lower their LDL-cholesterol do better than similar patients who have not.

The Case for OTC Simvastatin

Despite a strong body of evidence supporting the safe and effective use of statins, pharmaco-epidemiological studies in many countries have shown that statins are under-prescribed, sometimes perhaps because of cost restrictions. In addition, even when prescribed, levels of patient uptake and compliance may

vary. A further key, but underestimated issue is the lack of willingness of people potentially at risk to actually consult their doctor to be assessed for cardiovascular risk in the first instance. It is therefore clear that many potential candidates for statin treatment are either untreated or under treated.

The use of a low dose statin in a pharmacist supervised OTC setting represents a new model for OTC drug use and the role that pharmacists can play in this environment. Unlike conventional OTC treatments that are aimed at short-term, self-limiting conditions readily recognised by consumers, statin therapy requires ongoing treatment for a chronic condition that requires healthcare professional intervention for diagnosis and monitoring. Put in different terms, this model seeks group benefit while trying to minimise individual risk.

Treatment Gap for Statin Therapy in New Zealand

The use of OTC statins has been proposed as a new strategy to address the 'treatment gap' between those patients who could benefit from taking a cholesterol lowering medicine and those who actually receive one. Estimates based on PHARMAC data suggest that as many as 340,000 New Zealanders may potentially consitute this gap. Measures targeted at this group can only strengthen the efforts to reduce the burden of CHD, particularly in terms of primary prevention.

A pharmacist supervised OTC simvastatin strategy aligns well with the focus on primary prevention of cardiovascular disease in the Cardiovascular Action Plan, developed by the New Zealand Ministry of Health. A number of Public Health benefits and benefits to New Zealand consumers can therefore be anticipated from a reclassification of simvastatin 10 mg to Restricted Medicine status. These are highlighted in Table 1, included in this Executive Summary.

International Regulatory Status

Recent decisions by international regulatory authorities also provide support for the reclassification of simvastatin 10 mg in New Zealand.

In 2004, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK decided to reclassify simvastatin 10 mg as a Category P OTC medicine. The Agency recognised the favourable benefit to risk profile for low dose simvastatin for treating patients at moderate risk of CHD. The reclassification is intended to be an effective public health intervention to reduce the burden of CHD in the UK.

In January 2005, a Joint Advisory Committee from the Food and Drug Administration in the US considered whether low dose lovastatin (20 mg) should be approved for OTC use (without pharmacist intervention) for treating patients at moderate risk of CHD. The 25 Committee members voted unanimously that:

- The target population did merit treatment with a statin to lower cholesterol and thereby reduce the risk of heart disease,
- An adequate rationale was provided for the use of low dose lovastatin in the target population,
- Liver function testing was not required before or during treatment, and
- The risk of muscle toxicity with low dose lovastatin in the target population was acceptable for an over-the-counter drug.

The lovastatin submission was rejected by the FDA Committee, primarily because of concerns raised regarding the ability of consumers to adequately

self-select and self-manage statin treatment. It is critical to note that this proposed switch in the US was to the equivalent of New Zealand GSL status (there being only 2 relevant classifications in the US – prescription and general sales medicines).

In addition, in May 2004, the Medicines Classification Committee rejected a submission to reschedule simvastatin 10mg to Pharmacy Only Medicine status in New Zealand (as opposed to the Restricted Medicine status proposed in this application).

The GSKCH application takes account of the factors relevant to the approval of simvastatin 10mg in the UK, as well as the US and New Zealand rejections. The proposed strategies to address these factors are summarised in Tables 1 and 2 in this Executive Summary, and are further elaborated in the body of the submission.

The Role of the Pharmacist

Under GSKCH's proposal, New Zealand consumers would not self-select OTC simvastatin treatment. The reclassification of simvastatin to Restricted Medicine status mandates the intervention of a Pharmacist, whom with the aid of an appropriate assessment protocol and algorithm, will be able to decide the appropriate course of action, which may be treatment with simvastatin 10 mg, only life style advice, or referral to a doctor for further investigation. This situation is not unlike the UK model for simvastatin 10mg where Pharmacist intervention is also mandatory.

Numerous studies from a range of countries have demonstrated the benefits of pharmacist intervention in the management of patients with chronic diseases,

particularly high cholesterol. Pharmacists have been shown to help patients manage their lipid levels and help increase their awareness of CHD risk factors and possible treatment side effects. In addition, pharmacists have been shown to play a key role in helping improve compliance to treatment.

As a consequence of their ready accessibility and credibility among consumers, pharmacists would be ideally and uniquely positioned to facilitate the effective use of an OTC low dose simvastatin. In this regard, GSKCH is developing a comprehensive range of training and educational materials for pharmacists and consumers, in conjunction with relevant stakeholder bodies in New Zealand.

Training and Educational Strategies and Materials

A central message for any training and educational material is that low dose OTC simvastatin treatment is only one of a number of strategies that a patient should adopt to reduce the risk of CHD. This message is consistent with those communicated by other public health stakeholders in New Zealand such as the NZ National Heart Foundation.

In line with this, GSKCH is developing a multi-faceted programme focussing on lifestyle modification, the importance of health professional consultation and compliance to treatment regimens. This programme will be developed and implemented in consultation with key external stakeholders and professional bodies.

Importantly, GSKCH has a successful track record of working with New Zealand public health groups, pharmacists, doctors and consumers on the health improvement initiatives relating to the appropriate use of OTC medicines, including smoking cessation and low dose aspirin programmes.

In addition, GSKCH is undertaking a programme of label and Consumer Medicines Information leaflet comprehension studies that will examine Pharmacists' and consumers' abilities to select and use the product correctly. GSKCH have been leaders in the Australasian OTC medicines sector with the implementation of consumer focussed labelling and recently won the inaugural Australian National Prescribing Service Quality Use of Medicines for Industry for their work on the Panadol label. Whilst this programme is not perfectly predictive of consumer behaviour, it will provide valuable data which will be used to optimise the product labelling prior to final marketing. In addition, GSKCH will monitor utilisation patterns following launch to help ensure safe and appropriate usage of simvastatin 10mg.

Conclusion

In summary, CHD is a major public health burden in New Zealand. The epidemiological, medical and financial consequences of CHD demand more effective disease management strategies. Numerous studies and recent discussions by international regulatory authorities highlight the favourable benefit to risk profile of low dose statins for patients at moderate risk of CHD. In addition to lifestyle modifications, low dose simvastatin treatment could reduce the risk of CHD in mild to moderate risk patients.

The reclassification of simvastatin 10 mg from a Prescription Medicine to a Restricted Medicine, coupled with effective pharmacist intervention, would provide a new strategy for reducing the public health burden of CHD in New Zealand.

Table 1: The Consumer and Public Health Benefits of OTC Simvastatin.*

Consumer Benefits	Public Health Benefits
Easier access** to a lipid-lowering therapy, with a well established and favourable efficacy and safety profile.	The potential to decrease the incidence of CHD in New Zealand.
The potential to reduce the risk of CHD in individuals with a 5 to 15% risk of suffering from a cardiovascular event (non-fatal and fatal) within five years.	The potential to reduce the financial burden on the New Zealand health budget as a result of enhancing the primary prevention of CHD.
Enhanced interaction between consumers, pharmacists and general practitioners. Pharmacists will encourage consumers to interact appropriately with their doctor.	Increased general awareness of the risk factors for CHD and the lifestyle and treatment strategies that can be used to lower the risk of CHD.
Additional opportunities for counselling to assist lifestyle behaviour changes that can contribute to reducing the risk of CHD.	The potential to decrease the incidence of CHD in New Zealand
Identification of consumers who have a high risk of CHD. These patients, who would <u>not</u> be suitable for simvastatin 10mg therapy, could be identified early and directed to consult their general practitioner for more aggressive lipid-lowering management.	The potential to decrease the incidence of CHD in New Zealand The potential to reduce the financial burden on the New Zealand health budget as a result of enhancing the primary prevention of CHD

** Further details of the anticipated benefits are provided in Section 4.1.1.*

***The reference to easier access in this table refers to overcoming the barrier to visiting a GP and does not relate to any financial hurdles.*

Table 2: Summary of strategies to address potential concerns regarding reclassification of simvastatin*

Potential Concern	Proposed Strategy
Identifying the target population (mild to moderate risk)	• The proposed CHD Assessment Algorithm and Pharmacy Protocol have been modeled on the NZ Cardiovascular Risk Calculator. Consideration has been given to a number of risk factors and the algorithm and protocol address consumers' medical history.
Inability of pharmacists to identify the 'mild to moderate risk' population suitable for simvastatin 10mg treatment.	• The proposed CHD Assessment Algorithm and Pharmacy Protocol will be provided to pharmacists to assist them in identifying consumers CHD risk. Pharmacists will be trained on how to use the algorithm and protocol and hence to direct consumers toward the most appropriate management strategies. • The protocol will enable pharmacists to refer consumers classified at high risk of CHD to consult their general practitioner.
Inappropriate use of simvastatin 10mg by consumer (e.g. under- or over-treatment).	• Pharmacists will reinforce the need to take the appropriate dose of the product and the importance of treatment compliance to avoid the risk of under-treatment. • Over-treatment does not present an immediate safety concern. Consumers will be informed to seek medical advice in the case of an overdose.
Undue emphasis on cholesterol levels as being the major risk factor for intervention	• Consumers will be informed through Pharmacist advice, Consumer Medicines Information and other educational material that treatment is only one aspect of a comprehensive management strategy for improving cardiovascular health.

Potential Concern	Proposed Strategy
Risk of not achieving clinical benefit with 10mg simvastatin.	• Consumers will be required to test cholesterol levels approx 6 weeks after initiation of OTC treatment to ensure the appropriate management strategy has been instigated. Cholesterol will be monitored annually there after. These details are captured on a "patient card" (see Appendix 8 for draft).
Risk of identifying or delaying treatment for serious adverse events related to simvastatin.	• Pharmacists will be trained regarding the adverse drug reactions associated with simvastatin and how to manage these reactions. • Pharmacists will ascertain if the consumer has experienced any symptoms (including hypersensitivity) or shown any signs of adverse reactions to simvastatin (particularly muscle weakness). • The Consumer Medicine Information sheet and the trained pharmacist will help to educate consumers about the signs and symptoms of adverse reactions to simvastatin. • Pharmacists and consumers will be educated to make the consumer aware of the importance of immediately stopping medication and seeking medical attention if the consumer experiences muscle symptoms or symptoms indicative of liver disease.

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2 ** Further details of the proposed strategies are provided in Table 1*