



22 April 2016

Dear Review Committee,

Sanofi, an integrated global healthcare leader, discovers, develops and distributes therapeutic solutions focused on patient and consumer needs. We are proud to be the most diversified healthcare company in Australia and New Zealand.

As one of Australia's largest pharmaceutical suppliers, Sanofi continues to develop innovative treatments for diseases such as diabetes, cancer and heart disease. In the area of cardiovascular disease (CVD), [REDACTED]

[REDACTED] In this context, we welcome the opportunity to provide the following response to the Post-Market Review of Ezetimibe.

Cardiovascular disease and dyslipidaemia are a major cause of morbidity and mortality

Cardiovascular disease (CVD) was the underlying cause of 43,946 Australian deaths in 2012, which represents 30% of all deaths, and places CVD as the leading cause of death in Australia.¹ Atherosclerotic CVD was a major component of CVD deaths with 46% due to coronary heart disease (CHD) and 19% due to stroke. Dyslipidaemia is a prevalent and modifiable risk factor for atherosclerotic CVD and treatment of dyslipidaemia is an important element of actions to prevent CVD and associated deaths.²

The relationship between plasma lipids and CVD has been recognised for over 50 years.^{3,4} Since this time clinical management guidelines for dyslipidaemia have evolved to reflect the growing body of evidence in this area.^{2,5-13} Lipid management guidelines have progressed in three main areas. First, patient selection for lipid treatment has moved away from simple consideration of baseline lipid levels toward a cardiovascular (CV) risk based approach. Second, LDL-C has been increasingly recognised as the primary lipid treatment target lipid treatment in patients with high CV risk. Third, LDL-C treatment targets have become progressively lower.

During this time statins have become recognised as the first line treatment for dyslipidaemias. Non-statin treatments include ezetimibe, fibrates and bile acid sequestrants (BAS) have become established as important second-line therapies, as add on to statin for patients who are unable to achieve treatment targets, or for those who are unable to tolerate statins.^{2,8,12} Ezetimibe is the predominant non-statin therapy reflecting the focus on lowering LDL-C as the primary treatment target and the poor tolerability of other options, such as BAS.^{12,14}

Current lipid treatment options together with advances in treatment and diagnosis of CVD have contributed to the improvement in CVD related mortality, with CVD mortality declining by 71% for men and 67% for women since 1981.¹⁵ Despite ongoing advances CVD remains the leading cause of death in Australia.¹ In particular, there remains a population of patients with high CV risk who are unable to achieve LDL-C targets with existing treatment options.¹⁴ Recent US guidelines describe new therapies which offer greater reduction in LDL-C and may add to the available treatment options in the future for selected patients with high CV risk.¹⁶

Progression of absolute cardiovascular (CV) risk based approach

Prior to 2001 the National Heart Foundation Guidelines contained recommendations on both initiation points for lipid-modifying therapy and target lipid levels.⁵ However, it was increasingly recognised that cholesterol levels considered in isolation of patients other risk factors may be a poor guide to the clinical need for treatment, as the benefit of lipid treatment is a function of both the achieved LDL-C reduction and the patient's underlying CV risk. The guidelines released in 2001 defined treatment



targets according to CV risk. High CV risk was described as the presence of existing CV disease; conditions such as diabetes that were known to increase CV risk; a Framingham based risk score; and finally risk factors counting together with cholesterol levels. This approach to defining the need for lipid treatment primarily by assessment of a patient's CV risk has been carried through and refined in subsequent guidelines developed by the National Vascular Disease Prevention Alliance.^{2,13} Patients currently defined as high risk within Australian guidelines are those with:

- Existing CVD
- Diabetes and age >60 years
- Diabetes with microalbuminuria (> 20 mcg/min or urinary albumin:creatinine ratio >2.5 mg/mmol for males, >3.5 mg/ mmol for females)
- Moderate or severe chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate [eGFR] <45 mL/min//1.73 m²)
- A previous diagnosis of familial hypercholesterolaemia
- Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- Serum total cholesterol >7.5 mmol/L
- Greater than 15% risk of CVD within the next 5 years calculated by Framingham Risk Equation

LDL-C is recognised as the primary treatment target

Guidance to reduce hyperlipidaemia with diet and other interventions has existed since associations were observed between both plasma lipoprotein fractions and dietary fat with heart disease in the 1950s.^{3,4} Since this time data from epidemiological studies, such as MRFIT and Framingham, have demonstrated a strong association between hypercholesterolaemia and heart disease.^{17,18} Associations between and CV events and an inverse association with HDL-C and CV events has also been identified. In the 1980s and 1990s interventional data from studies with statins, BAS and ileal bypass demonstrated that reduction in LDL-C levels was associated with reduced development and progression of CV disease.¹⁹⁻²¹ Recognising this growing evidence the 2001 NHF/CSANZ Lipid management guidelines included *"an increased emphasis on low-density lipoprotein cholesterol (LDL-C) as the major atherogenic component of plasma"*.⁵ This focus on LDL-C over other lipid fractions remains in current guidelines, including the Australian National Vascular Disease prevention alliance guidelines for absolute cardiovascular disease risk 2012, and the Therapeutic Guidelines Cardiovascular Version 6 2012, which state *"LDL-C remains the primary treatment target"*.^{2,12}

Cholesterol treatment targets have become progressively lower

Treatment targets for LDL-C have been a feature of the majority of guidelines for many years.^{5,10} Observational studies demonstrating an association between cholesterol levels and CV disease have contributed to determination of cholesterol treatment targets.²²⁻²⁴ However, the treatment targets have been primarily informed by studies comparing statins to placebo or higher vs lower intensity statin dose.² These studies have not been designed specifically to determine what LDL-C target should be and targets described in guidelines have reflected the lipid levels achieved in the higher intensity treatment arms of studies.²⁵ The 2001 NHFA Guidelines recommended that LDL-C concentration should be reduced to 2.5 mmol/L in secondary prevention and to 3.0 mmol/L in primary prevention.⁵ As evidence has accumulated to support the safety and benefit of achieving lower levels of LDL-C, target levels have been lowered. Current targets are 1.8 mmol/L in patients with established coronary heart disease, and 2.0mmol/L in primary prevention patients.^{2,8} In the international context the current Australian treatment targets are lower for primary prevention patients than some other guidelines.^{26,27} As noted above, clinical trials have not specifically tested target lipid levels. In 2013 the American College of Cardiology (ACC) and American Heart Association (AHA) developed guidelines which instead focused on the use of high intensity therapy to achieve a reduction of 30 to 50% of LDL from baseline.²⁸ More recently the ACC/AHA have released guidance for the role of non-statin therapies and have returned to the use of treatment targets.¹⁶ Regardless of the way treatment intensity is



defined all guidelines are consistent in recommending aggressive management of LDL-C in patients at high risk of CVD.^{2, 12, 16, 26-28}

Statins are the first line treatment

The Cholesterol Treatment Trialists Collaboration has performed individual patient data meta-analyses using data from 26 randomised statin trials involving 170,000 participants.²¹ The meta-analysis was the foundational analysis for the relationship between LDL-C and CV risk reduction and identified a 22% relative reduction in major vascular events for every 1.0 mmol/L reduction of LDL-C (rate ratio [RR] 0.78, 95% CI 0.76–0.80; $p < 0.0001$). The result was consistent across different patient subgroups studied, including those with LDL-C lower than 2 mmol/L on the less intensive or control regimen. All-cause mortality was reduced by 10% per 1.0 mmol/L LDL reduction (RR 0.90, 95% CI 0.87–0.93; $p < 0.0001$), largely reflecting significant reductions in deaths due to coronary heart disease (RR 0.80, 99% CI 0.74–0.87; $p < 0.0001$) and other cardiac causes (RR 0.89, 99% CI 0.81–0.98; $p = 0.002$). Statins are now clearly defined as first line therapy in Australian treatment guidelines for management of patients with CVD and those at risk of developing CVD.^{2, 8, 12}

Non-statin treatments for CVD

Statins are generally effective and well tolerated. However, not all patients can achieve adequate reduction in LDL-C using statins. Failure to achieve LDL-C targets may be due to high baseline LDL-C, inadequate response to treatment, inadequate dose or intolerance.^{16, 29, 30}

Non-statin therapies play an important role as add on to statin for patients who are unable to achieve treatment targets, or for those who are unable to tolerate statins.^{2, 8, 12} Ezetimibe is the predominant non-statin therapy reflecting the focus on LDL-C as the primary treatment target and the poor tolerability of other options, such as BAS.^{12, 14} Fibrates lower TG and also give a small reduction in LDL-C, the use of fibrates is limited.^{12, 14} Niacin and BAS are poorly tolerated and rarely used.¹²

Recently, new evidence from the IMPROVE-IT study, has confirmed the benefit of adding ezetimibe to statins to achieve further reduction in LDL-C.³¹ In the IMPROVE-IT study ezetimibe was compared with placebo as add on therapy to statin following acute coronary syndrome (ACS). Ezetimibe achieved a reduction in LDL-C of 0.4mmol/L compared with placebo with a statistically significant reduction in major CV events. The Kaplan–Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin–ezetimibe group, as compared with 34.7% in the simvastatin-placebo group (HR, 0.936; 95% CI, 0.89 to 0.99; $P = 0.016$). Importantly, the relative reduction in CV events is as predicted based on the achieved LDL-C reduction and the relationship between LDL-C reduction and CV events observed in statin studies. The IMPROVE-IT result has been described as proof that LDL-C is a causal factor of CVD and reducing LDL-C reduces CVD.³¹

Ongoing clinical need

Growing awareness of the importance of lowering LDL-C and appropriate use of existing treatments has contributed to a significant reduction of CV death rates in Australia over the last 30 years.¹⁵ However, CVD remains the major cause of death and not all patients can achieve adequate reduction of LDL-C with current therapies. A recent BEACH study reported that mean LDL-C of very high CV risk patients treated with high intensity statin was 2.27 mmol/L and for patients treated with ezetimibe and high intensity statin mean LDL-C was 2.31 mmol/L.¹⁴ Despite the availability of programs aimed at improving use of existing therapies, such as cardiac rehabilitation programs, patients are still not meeting treatment targets.³³ New therapies which offer greater reduction in LDL-C may contribute to further reduction in CV death rates in Australia.

In summary statins, a proven and effective first line treatment, are not sufficient to adequately reduce LDL-C for some patients due to high baseline LDL-C, intolerance or poor response. Ezetimibe is



established as a second line option achieving additional reductions in LDL-C alone in combination with a statin for patients. There remains a population of patients with high CV risk who are unable to adequately achieve LDL-C targets with these current treatment options resulting in potentially preventable cardiovascular disease. New therapies which offer greater reduction in LDL-C may become additional treatment options in the future for selected patients with high CV risk.¹⁶

Patient management and support across the healthcare ecosystem

In line with the National Medicines Policy and the tenet of Quality Use of Medicines, it is important to acknowledge the place that lifestyle modification plays in aiding the reduction of cholesterol amongst all people living with elevated cholesterol. Unfortunately a great percentage of people will need more than just lifestyle (diet and exercise) adjustment to reduce cholesterol to target levels.

Australia is very fortunate to have a range of pharmaceutical treatment options that will compliment lifestyle modification in reducing cholesterol. All stakeholders involved in CV disease management (including patients themselves) must take a holistic approach to the challenge of reducing cholesterol and ultimately the burden of CV disease in Australia. Therefore, we believe strategies to improve patient outcomes centred on improving adherence and maximising collaborative care is a vital consideration as part of this review. In fact, the importance of appropriate education, information and support to facilitate the management of health by consumers and clinicians is common to all areas.

The ability for clinicians (and ultimately patients) to have access to innovative and broad ranging treatment options is imperative to achieving targeted individual patient and population reductions in CV morbidity and mortality. To maximise the value of the use of these medicines in the appropriate individuals it is critical this review considers recommendations which support the broader health relationship and do not focus solely on the role medications.

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