Technology Guidance

PCSK9 inhibitors

for treating hypercholesterolaemia

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Evolocumab 140 mg/mL solution for injection in prefilled autoinjector for treating:
  - non-familial hypercholesterolaemia (non-FH) or mixed dyslipidaemia, with atherosclerotic cardiovascular disease (ASCVD) and additional risk factors and LDL-c level above 1.8 mmol/L despite maximal tolerated lipid-lowering therapy (LLT) for at least 12 weeks; or
  - heterozygous familial hypercholesterolaemia (HeFH), with ASCVD and LDL-c level above 1.8 mmol/L despite maximal tolerated LLT for at least 12 weeks; or
  - HeFH, without ASCVD, and LDL-c level above 2.6 mmol/L despite maximal tolerated LLT for at least 12 weeks; or
  - homozygous familial hypercholesterolaemia (HoFH) with LDL-c level above 1.8 mmol/L despite maximal tolerated statin-lowering therapy for at least 12 weeks.

Funding status

Evolocumab 140 mg/mL solution for injection in prefilled autoinjector is recommended for inclusion on the MOH Medication Assistance Fund (MAF) for the abovementioned indications from 1 November 2023.

The dose of evolocumab for the treatment of non-FH or mixed dyslipidaemia and HeFH recommended for subsidy is **140 mg every 2 weeks**. The dose restriction does not apply to HoFH.

Evolocumab should be used in line with the additional clinical criteria listed in the Annex.

MAF assistance **does not** apply to any formulations or strengths of alirocumab or inclisiran for treating hypercholesterolaemia.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the June 2023 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (alirocumab, evolocumab and inclisiran) for treating non-familial hypercholesterolaemia (non-FH) and heterozygous familial hypercholesterolaemia (HeFH). Evidence for evolocumab for treating homozygous familial hypercholesterolaemia (HoFH) was also considered. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions and patient experts from local patient and voluntary organisations. Published clinical and economic evidence for each PCSK9 inhibitor was considered in line with their registered indications.

1.2. Alirocumab and inclisiran were not evaluated for treating HoFH, as they were not approved by the Health Sciences Authority for this indication at the time of evaluation.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. Hypercholesterolaemia is an established causal risk factor for atherosclerotic cardiovascular disease (ASCVD). International clinical practice guidelines (CPGs) recommend stringent target LDL-c levels for patients at high and very high risk of developing ASCVD. However, not all patients are able to achieve these targets despite treatment with maximal tolerated lipid-lowering therapy (LLT; i.e. high-intensity or maximally-tolerated statin in combination with ezetimibe).

2.2. The Committee noted that PCSK9 inhibitors such as the monoclonal antibodies (mAbs; alirocumab and evolocumab) and a small-interfering RNA (siRNA; inclisiran) have different mechanisms of action to other commonly used, subsidised treatments for hypercholesterolaemia such as statins and ezetimibe.

2.3. In line with international CPGs, the Committee noted that PCSK9 inhibitors are used in the third-line setting as add-on to maximal tolerated LLT. The Committee noted that, locally, PCSK9 inhibitors are used in patients unable to achieve target LDL-c levels despite maximal tolerated LLT who are from the following populations:

- non-FH with ASCVD and additional risk factors;
- HeFH with or without ASCVD; and
- HoFH.

2.4. The Committee considered testimonials from local patient experts about their lived experiences with hypercholesterolaemia and the treatments they have received. The Committee noted that the patient experts were all receiving statins, with or without other lipid-lowering therapies, as their primary treatment, and considered that statins worked well in lowering LDL-c levels, were easy to take, and generally well tolerated. None of the patients had experience with any PCSK9 inhibitors; however, they expressed concern about their potential side-effect profile and cost compared to oral treatments.

Clinical effectiveness and safety

3.1. The Committee heard that alirocumab and evolocumab significantly reduced the risk of primary composite cardiovascular (CV) outcomes in patients with ASCVD. Results from phase III randomised, placebo-controlled cardiovascular outcomes trials (ODYSSEY OUTCOMES and FOURIER) reported a hazard ratio of 0.85 (95% CI 0.78 to 0.93, $p<0.001$) for alirocumab and a hazard ratio of 0.85 (95% CI 0.79 to 0.92, $p<0.001$) for evolocumab. While there was no apparent difference in mortality risk for either medication compared with placebo, the Committee noted that the follow-up period in both trials was relatively short. CV outcomes data for inclisiran was not available at the time of evaluation.

3.2. The Committee noted that all three PCSK9 inhibitors (alirocumab, evolocumab, or inclisiran) added to statin, with or without other LLT, resulted in a statistically significant LDL-c reduction across various randomised-controlled trials (RCTs) compared with placebo. The RCTs enrolled populations with different ASCVD risks including (i) non-FH with ASCVD, (ii) HeFH with or without ASCVD, and (iii) HoFH (for evolocumab trials only).

3.3. In terms of safety, the Committee noted that PCSK9 inhibitors were associated with a higher incidence of injection-site reactions compared with placebo. However, there were no significant safety issues identified across the studies, and the development of neutralising antibodies against the PCSK9 mAbs was rare.

3.4. There were no head-to-head studies comparing alirocumab, evolocumab and inclisiran with each other for CV and LDL-c outcomes. Between alirocumab and

evolocumab, the Committee reviewed results of indirect treatment comparisons (ITC) considered by PBAC (Australia) and agreed it was reasonable to consider alirocumab (at the higher dosing regimen) non-inferior to evolocumab based on LDL-c reduction. However, ITC results for CV outcomes were considered non-definitive due to major exchangeability issues between the trials, including differences in definitions of CV endpoints and trial follow-up duration. Despite the limited data to assess comparative safety, the Committee accepted it might be reasonable to consider PCSK9 mAbs similar in terms of safety.

3.5. The Committee noted results from a network meta-analysis (NMA) submitted to NICE (UK) which showed inclisiran was associated with an LDL-c reduction that was marginally less than with the PSCK9 mAbs, although the difference was not statistically significant. The Committee noted heterogeneity issues between the various trials may have limited the exchangeability of outcomes in the NMA. Overall, the Committee agreed it was uncertain whether inclisiran could be considered non-inferior to the PCSK9 mAbs. The ongoing cardiovascular outcomes trials ORION-4 and VICTORIAN-2P will provide more certainty on the extent of its cardiovascular benefits.

Cost effectiveness

4.1. In view of comparable efficacy and safety, the Committee agreed that a cost-minimisation approach was appropriate to assess the cost-effectiveness of PCSK9 mAbs, based on equi-effective doses of alirocumab 150 mg (every 2 weeks), evolocumab 140 mg (every 2 weeks) and evolocumab 420 mg (every month). The Committee also noted an evaluation by PBAC (Australia), which considered that a lower price for inclisiran would be required to address the uncertainty in the non-inferiority assessment.

4.2. The Committee considered that evolocumab 140 mg (every 2 weeks), which had the lowest cost, was the most cost-effective option. The Committee also noted that the price of evolocumab was comparable to prices in overseas reference jurisdictions, coupled with an adequate proposal to manage the uncertainty of the overall budget impact.

4.3. Overall, the Committee agreed that evolocumab was likely to be considered an acceptable use of healthcare resources when used locally as an add-on to maximal tolerated LLT for treating (i) non-FH with ASCVD and additional risk factors, (ii) HeFH with or without ASCVD and (iii) HoFH, in line with recommendations by overseas reference HTA agencies.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million in the first year, and between SG$3 million and SG$5 million in the fifth year of listing evolocumab on the Medication Assistance Fund (MAF).

Additional considerations

6.1. The Committee heard that patients with mixed dyslipidaemia are treated similarly to hypercholesterolaemia. Hence, should PCSK9 inhibitors be recommended for MAF subsidy, it was considered reasonable to extend the listing to this population.

Recommendations

7.1. Based on available evidence, and given its clinical need and acceptable clinical and cost-effectiveness, the Committee recommended evolocumab 140 mg/mL solution for injection in prefilled autoinjector (restricted to 140 mg every 2 weeks dosing) be listed on the MAF for treating (i) non-FH or mixed dyslipidaemia with ASCVD and additional risk factors, (ii) HeFH with or without ASCVD and (iii) HoFH. Evolocumab should be used in line with the additional clinical criteria listed in the Annex.

7.2. The Committee recommended not listing alirocumab and inclisiran on the MOH List of Subsidised Drugs due to unacceptable cost-effectiveness compared with evolocumab.

Annex

MAF clinical criteria for evolocumab

Evolocumab 140 mg/mL solution for injection in prefilled autoinjector for treating:

- non-familial hypercholesterolaemia (non-FH) or mixed dyslipidaemia, with atherosclerotic cardiovascular disease (ASCVD) and additional risk factors and LDL-c level above 1.8 mmol/L despite maximal tolerated lipid-lowering therapy (LLT) for at least 12 weeks; or
- heterozygous familial hypercholesterolaemia (HeFH), with ASCVD and LDL-c level above 1.8 mmol/L despite maximal tolerated LLT for at least 12 weeks; or
- HeFH, without ASCVD, and LDL-c level above 2.6 mmol/L despite maximal tolerated LLT for at least 12 weeks; or
- homozygous familial hypercholesterolaemia (HoFH) with LDL-c level above 1.8 mmol/L despite maximal tolerated statin-lowering therapy for at least 12 weeks.

Atherosclerotic cardiovascular disease is defined as

- the presence of symptomatic coronary artery disease (i.e. prior myocardial infarction, prior revascularisation procedure, angina associated with demonstrated significant coronary artery disease [i.e. 50% or greater stenosis in 1 or more coronary arteries on imaging]), or positive functional testing (e.g. myocardial perfusion scanning or stress echocardiography); or
- the presence of symptomatic cerebrovascular disease (i.e. prior ischaemic stroke, prior revascularisation procedure, or transient ischaemic attack associated with 50% or greater stenosis in 1 or more cerebral arteries on imaging); or
- the presence of symptomatic peripheral arterial disease (i.e. prior acute ischaemic event due to atherosclerosis, prior revascularisation procedure, or symptoms of ischaemia with evidence of significant peripheral artery disease [i.e. 50% or greater stenosis in 1 or more peripheral arteries on imaging]).

Additional risk factors include any of the following:

- atherosclerotic disease in two or more vascular territories (i.e. coronary, cerebrovascular or peripheral vascular territories); or
- severe multi-vessel coronary heart disease defined as at least 50% stenosis in at least two large vessels; or
- at least two major cardiovascular events (i.e. myocardial infarction, unstable angina, stroke or unplanned revascularisation) in the previous 5 years; or
- diabetes mellitus with microalbuminuria; or
- diabetes mellitus and be aged 60 years or more; or
- Thrombolysis in Myocardial Infarction (TIMI) risk score for secondary prevention of 4 or higher.

For homozygous familial hypercholesterolemia, the condition must have been confirmed by genetic testing; OR the condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 7.

For heterozygous familial hypercholesterolemia, the condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6.

Maximal tolerated lipid-lowering therapy refers to:

- treatment with maximum recommended dose of atorvastatin (40-80 mg daily) or rosuvastatin (20-40 mg daily) or the maximum tolerated dose of atorvastatin or rosuvastatin, in combination with ezetimibe; or
- patient developed clinically important product-related adverse events[1] necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; or
- patient is contraindicated to a statin as defined in the HSA-approved Product Information.

Maximal tolerated statin-lowering therapy refers to:

- treatment with maximum recommended dose of atorvastatin (40-80 mg daily) or rosuvastatin (20-40 mg daily) or the maximum tolerated dose of atorvastatin or rosuvastatin; or
- patient developed clinically important product-related adverse events[1] necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; or
- patient is contraindicated to a statin as defined in the HSA-approved Product Information.

[1]**A clinically important product-related adverse event** is defined as follows:

- severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or
- myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements, and which is unexplained by other causes; or
- unexplained, persistent elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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