**Cost-effectiveness of inclisiran (Leqvio®) for the treatment of adults with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet.**

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of inclisiran (Leqvio®). Following assessment of the Applicant's submission, the NCPE recommends that inclisiran (Leqvio®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Novartis Ireland Ltd) Health Technology Assessment of inclisiran (Leqvio®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

**About the National Centre for Pharmacoeconomics**

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

**National Centre for Pharmacoeconomics** **March 2022**

**Summary**

In July 2021, Novartis Ireland Ltd submitted a dossier of clinical, safety, and economic evidence in support of inclisiran (Leqvio®) for the treatment of adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet. Novartis Ireland Ltd are seeking reimbursement in the hospital setting. Final data was submitted by the Applicant in November 2021.

Hypercholesterolaemia is characterised by elevated levels of low-density lipoprotein cholesterol (LDL-C) in the blood. It is associated with an underlying genetic cause: either a single genetic defect (familial) or, more commonly, by the interaction of several genes with dietary and other lifestyle factors (non-familial). Dyslipidaemia is characterised by elevated levels of LDL-C, triglycerides, or both. Inclisiran is indicated, as an adjunct to diet, for the treatment of primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

The first step in the treatment pathway involves assessment of overall cardiovascular (CV) risk. This will determine target LDL-C treatment goals. Non-pharmacological treatment measures include improved diet, exercise, and smoking cessation. Pharmacological treatment should be considered for secondary prevention in all patients with established atherosclerotic disease (ASCVD), and for primary prevention in individuals without a history of ASCVD who are considered to be elevated risk. ASCVD includes previous myocardial infarction, ischaemic stroke, unstable angina, and peripheral arterial disease. First-line pharmacological treatment is with a high potency statin (for example, atorvastatin or rosuvastatin) at the maximum tolerated dose (MTD). If target LDL-C levels fail to be achieved despite MTD statin therapy, the cholesterol absorption inhibitor, ezetimibe, may be added. If target LDL-C levels are still not achieved with MTD statin and ezetimibe, addition of a proprotein convertase subtilisin/kexin (PCSK9) inhibitor may be considered. In Ireland, the PCSK9 inhibitors (alirocumab and evolocumab) are reimbursed for patients who satisfy pre-requisite eligibility criteria subject to a Health Service Executive (HSE) managed access programme.

Inclisiran is a first-in-class, small interfering ribonucleic acid (siRNA). It acts in the liver, where it interferes with ribonucleic acid to limit production of the enzyme PCSK9.

Preventing PCSK9 production lowers LDL-C levels. Inclisiran is formulated as a 284mg per 1.5ml solution for injection in a pre-filled syringe (PFS). The recommended dose is 284mg once to start, then 284mg once at three months, and then 284mg once every six months thereafter. Inclisiran is administered by a healthcare professional via subcutaneous injection. Given the chronic nature of the condition, it is anticipated that the duration of treatment with inclisiran will be life-long, unless it is discontinued (for example due to adverse events or pregnancy).

The Applicant anticipates that inclisiran will be prescribed as a third-line treatment option following failure to achieve target LDL-C levels despite treatment with MTD statin therapy and ezetimibe. This is narrower than the product licence. Inclisiran, as an adjunct to diet, is indicated:

- In combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or
- Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

The Applicant considered the relevant comparators to be standard of care (SoC), which the Applicant defined as a population-specific mix of MTD statins (including no statin) and other lipid lowering drugs (primarily ezetimibe), and the PCSK9 inhibitors (alirocumab and evolocumab). Bempedoic acid, with and without ezetimibe, was also considered in a scenario analysis. Whilst the Review Group consider this to be appropriate, bempedoic acid is not currently reimbursed in Ireland. Consequently, cost-effectiveness analyses comparing inclisiran and bempedoic acid are not presented here.

## 1. Comparative effectiveness of inclisiran

Clinical evidence is available from the double-blind, placebo-controlled, phase III trials ORION-9, -10 and -11. Participants were required to have LDL-C levels ≥1.8mmol/L (≥2.6mmol/L for ORION-9) while receiving background maximally tolerated lipid-lowering therapy. The proportions of patients, in each subpopulation, receiving different forms of background lipid-lowering therapies informed the SoC comparator in the economic model. The population of ORION-9 was largely a heterozygous familial (HeFH), primary prevention population (participants were not required to have a history of ASCVD); the population of

ORION-10 was a secondary prevention population (all participants were required to have a history of ASCVD); the ORION-11 population was a mixed population where participants were required to have either a history of ASCVD or were ASCVD-risk equivalent (ASCVD-RE). Co-primary endpoints for all three trials were percentage change in LDL-C from baseline to Day 510 and time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. For both endpoints, across all three trials, inclisiran demonstrated approximately a 50% reduction in LDL-C levels relative to placebo in all cases; the results were statistically significant.

Direct comparative evidence for inclisiran versus the PCSK9 inhibitors and bempedoic acid (with and without concomitant ezetimibe) was not available. The Applicant generated indirect comparative evidence for these medicines by conducting a series of network meta-analyses (NMAs) with outcomes including change from baseline in LDL-C levels, safety, and discontinuation at 24-weeks. The Review Group identified several limitations to the Applicant's evidence synthesis. There was considerable heterogeneity between trials included in the NMA, particularly with respect to concomitant ezetimibe use, ASCVD history, and baseline LDL-C levels. The NMA further requires the assumption that relative treatment effects for all interventions are unaffected by background ezetimibe use. The Review Group regard this assumption as plausible but uncertain for some comparisons (notably, it has not been assessed for inclisiran), but unlikely to be valid for comparisons with ezetimibe (and bempedoic acid plus ezetimibe). While this assumption is a source of uncertainty potentially affecting all of the NMA results, a particular area of concern is that treatment effects from the NMA may not be generalisable to patients receiving ezetimibe as part of SoC, who make up a considerable proportion of patients in the economic model. The results of the NMAs suggest that inclisiran is more effective than bempedoic acid (in all analysed populations), and ezetimibe (in the ASCVD or ASCVD-RE populations). Across all the analyses, alirocumab and evolocumab demonstrated a numerically, but not statistically significant, benefit over inclisiran in reducing LDL-C levels. In the analyses of ASCVD or ASCVD-RE populations intolerant to statins, bempedoic acid plus ezetimibe also demonstrated a numeric, but not statistically significant, benefit over inclisiran.

## 2. Safety of inclisiran

Pooled analysis of the ORION-9, ORION-10, and ORION-11 studies indicates that similar proportions of patients treated with placebo and inclisiran- reported one or more treatment-emergent adverse events (77.3% and 78.0%, respectively). Overall, the incidence and type of common adverse drug reactions reported in the phase III clinical trials was comparable between the placebo and inclisiran arms. One exception was incidence of injection site reactions, which were reported by 8.2% of patients treated with inclisiran compared to 1.8% of patients treated with placebo.

## 3. Cost effectiveness of inclisiran

Cost-effectiveness was assessed, from the perspective of the HSE, using a Markov-model with lifetime horizon. Model cycle length was one year; a half-cycle correction was applied. Three subpopulations were included in the model:

- Adults with a history of ASCVD (ASCVD population);
- Adults with a history of HeFH who have not previously experienced a CV event (HeFH primary prevention population); and
- Adults who have not previously experienced a CV event but are at higher risk of doing so compared to the general population (Primary Prevention of patients at elevated risk [PPER] population)

For the PPER population, patients at elevated risk were defined as those having one or more of the following risk factors: type 2 diabetes; FH; ten-year risk of a CV event ≥20% (as assessed by Framingham Risk Score or equivalent). The ASCVD population was further subdivided according to ASCVD history. All patients in all subpopulations were assumed to have baseline LDL-C ≥2.6mmol/L despite treatment with MTD statin. The modelled intervention was inclisiran; the primary comparators included were SoC and the PCSK9 inhibitors (alirocumab and evolocumab). For the purpose of the assessment, the Applicant defined SoC as a population-specific mix of MTD statins and other lipid-lowering therapies (e.g. ezetimibe). The proportions of patients prescribed MTD statin therapy and ezetimibe as part of SoC varied depending on the subpopulation being modelled, and reflected the relevant subpopulation in the ORION clinical trials.

Patients entered the model in an initial health state with subsequent progression determined by the occurrence of further CV events. There were five core post-event states: revascularisation, unstable angina, non-fatal myocardial infarction, non-fatal ischaemic stroke, and death. Transition probabilities for the baseline risk of each CV event type were estimated using an unpublished observational study, conducted by the Applicant and which utilised UK based data. These baseline transition probabilities were subsequently adjusted for risk factors (such as age, baseline LDL-C, type 2 diabetes status, and sex) to align with the subpopulation being modelled. In the absence of CV outcome data for inclisiran, treatment effectiveness was modelled using change from baseline in LDL-C as a surrogate endpoint. Health outcomes were informed by EQ-5D-3L data taken from a systematic review of the published literature. In the economic model, health outcomes were expressed as quality adjusted life years (QALYs). Utility values were estimated by applying disease-specific multipliers to age- and sex-adjusted utilities. Costs and resources considered in the model encompassed drug acquisition, dispensing, and administration costs (where applicable); revascularisation costs and costs associated with management of CV events.

Economic models, similar to inclisiran, have previously been submitted to the NCPE in support of assessment of other cholesterol-lowering medicines. Whilst the structure of these models is generally considered appropriate, the Review Group did identify concerns. Lifetime CV risk in the SoC arm appears to differ considerably between economic models. Compared to the economic models for the PCSK9 inhibitors, the model for inclisiran predicts considerably higher risk in the ASCVD population, and considerably lower risk in the HeFH primary prevention population. Consequently, the modelled absolute treatment effects (incremental life years; incremental QALYs) of inclisiran and other interventions are higher in the ASCVD population and lower in the HeFH primary prevention population, compared with the economic models for the PCSK9 inhibitors. This leads to divergent cost-effectiveness results for the same intervention between the three models. It is not possible to assess which (if any) of the three models produce the most realistic predictions of long-term CV outcomes.

The Review Group were also concerned that modelled SoC did not align with the Applicant's proposed positioning of inclisiran in Irish clinical practice (that is as a third line treatment for patients failing to achieve target LDL-C levels despite treatment with MTD statin and

ezetimibe). It would be reasonable to expect that almost all patients would be prescribed ezetimibe. However, this accounted for only 51%, 10%, and 6% of patients in the HeFH primary prevention, ASCVD, and PPER populations, respectively. Finally, the Review Group had concerns that the model structure may overestimate the effect of lowering LDL-C on CV mortality in the long term. The reduced risk of non-fatal CV events leads to an additional reduction in the risk of CV death in the model. This has already been included implicitly in the direct effect of LDL-C on CV death applied in the model, resulting in double-counting. This may overestimate the QALY gain associated with inclisiran (and other interventions) relative to SoC.

Results of a pairwise analysis, comparing inclisiran versus SoC in the three subpopulations considered, are presented in Table 1 for the Applicant's base case and Table 2 for the NCPE-adjusted base case.

**Table 1: Results of the Applicant's base case pairwise cost-effectiveness analysis of inclisiran versus SoC in the three subpopulations presented in the economic model**

| Intervention | Total costs (€) | Total QALYs | Inc. costs (€) | Inc. QALYs | ICER vs SoC (€/QALY) |
|---|---|---|---|---|---|
| **ASCVD population** | | | | | |
| SoC (84% statins, 10% ezetimibe) | 12,538 | 6.82 | - | - | - |
| Inclisiran+SoC | 70,434 | 7.62 | 57,896 | 0.80 | **72,239** |
| **PPER population** | | | | | |
| SoC (77% statins, 6% ezetimibe) | 7,312 | 9.83 | - | - | - |
| Inclisiran+SoC | 79,799 | 10.48 | 72,487 | 0.66 | **110,444** |
| **HeFH primary prevention population** | | | | | |
| SoC (87% statins, 51% ezetimibe) | 6,599 | 13.83 | - | - | - |
| Inclisiran+SoC | 101,278 | 14.07 | 94,679 | 0.24 | **392,384** |

**ASCVD:** atherosclerotic cardiovascular disease; **HeFH**: heterozygous familial hypercholesterolemia; **ICER:** Incremental cost-effectiveness ratio; **Inc.**: incremental; **PPER:** primary prevention elevated risk; **QALY**: quality-adjusted life year; **SoC**: standard of care.
Figures in this table are rounded; calculations may not be directly replicable. A discount rate of 4% for costs and outcomes is applied.

**Table 2: Results of the NCPE-adjusted base case pairwise cost-effectiveness analysis of inclisiran versus SoC in the three subpopulations presented in the economic model**

| Intervention | Total costs (€) | Total QALYs | Inc. costs (€) | Inc. QALYs | ICER vs SoC (€/QALY) |
|---|---|---|---|---|---|
| **ASCVD population** | | | | | |
| SoC (84% statins, 10% ezetimibe) | 13,119 | 7.23 | - | - | - |
| Inclisiran+SoC | 72,242 | 7.94 | 59,123 | 0.71 | **83,426** |
| **PPER population** | | | | | |
| SoC (77% statins, 6% ezetimibe) | 7,519 | 9.99 | - | - | - |
| Inclisiran+SoC | 80,849 | 10.61 | 73,330 | 0.62 | **118,006** |

| | | | | | |
|---|---|---|---|---|---|
| **HeFH primary prevention population** | | | | | |
| SoC (87% statins, 51% ezetimibe) | 6,615 | 13.87 | | | |
| Inclisiran+SoC | 101,502 | 14.10 | 94,887 | 0.23 | **407,991** |

**ASCVD:** atherosclerotic cardiovascular disease; **HeFH**: heterozygous familial hypercholesterolemia; **ICER:** Incremental cost-effectiveness ratio; **Inc.**: incremental; **PPER:** primary prevention elevated risk; **QALY**: quality-adjusted life year; **SoC**: standard of care.
Figures in the table are rounded; calculations may not be directly replicable. A discount rate of 4% for costs and outcomes is applied.

The probability of cost-effectiveness of inclisiran compared to SoC was 0% across all three subpopulations at the €20,000/QALY and €45,000/QALY thresholds, under both the Applicant's base case and the NCPE's adjusted base case.

In Ireland, the PCSK9 inhibitors (alirocumab and evolocumab) are reimbursed for patients who satisfy pre-requisite eligibility criteria, subject to a HSE managed access programme. Cost-effectiveness analyses comparing both inclisiran and the PCSK9 inhibitors to SoC were conducted in the subpopulations eligible for the PCSK9 inhibitor managed access programme, with all three interventions returning broadly similar ICERs compared with SoC. However, in all subpopulation analyses, the PCSK9 inhibitor evolocumab was demonstrated to be the most cost-effective treatment option. Inclisiran had a higher ICER than evolocumab when both were compared with SoC, with evolocumab having demonstrated greater treatment benefit.

## 4. Budget impact of inclisiran

The price to wholesaler per pack of inclisiran is €2,850; each pack contains one 284mg pre-filled syringe. The cost per patient, to the HSE, for the first year of treatment with inclisiran is €8,080 excl. VAT (€10,046 incl. VAT); the annual treatment cost per patient to the HSE from year two onwards is €5,387 excl. VAT (€6,698 incl. VAT).

For the budget impact analysis, the Applicant only considered patients failing to achieve target LDL-C levels despite treatment with MTD statin and ezetimibe to be eligible for inclisiran therapy. This is a subpopulation of the product licence; budget impact estimates considering the broader population defined by the product licence would be higher. The Applicant also assumed that patients who are non-compliant with their statin and ezetimibe therapy would not be eligible for inclisiran. In the absence of supporting evidence, the Review Group did not consider this assumption to be reasonable. Furthermore, the Review

Group cautions that inclisiran might be considered for these patients because of its lower frequency of administration. The Applicant estimated that approximately 616 patients would be treated with inclisiran in year one, rising to 7,007 in year five. For NCPE-adjusted patient estimates, the assumption regarding non-compliant patients was removed. The NCPE estimated that approximately 881 patients would be treated with inclisiran in year one, rising to 10,010 in year five.

The Applicant estimated the gross budget impact for inclisiran to be €6.4 million in year one increasing to €55.2 million in year five, with the five-year cumulative gross budget impact estimated to be €149.7 million. The introduction of inclisiran is expected to result in some displacement of the PCSK9 inhibitors. The Applicant estimated the five-year cumulative net drug budget impact to be €117.7 million. Using NCPE-adjusted eligible patient numbers, the five-year cumulative gross and net drug budget impacts were estimated to be €213.8 million and €168.1 million, respectively. Commercial in confidence Patient Access Schemes, which are not included in this summary document, are in place for a number of comparators; the true net budget impact to the HSE will be higher than that presented here. The budget impact analyses for inclisiran are highly sensitive to eligible patient numbers, which are inherently uncertain.

## 5. Patient Organisation Submissions

No patient organisation submissions were received during the course of this assessment.

## 6. Conclusion

The NCPE recommends that inclisiran (Leqvio®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.