Cost-effectiveness of siponimod (Mayzent ®) for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of siponimod (Mayzent®). Following assessment of the Applicant's submission, the NCPE recommends that siponimod (Mayzent®) 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 Ltd) economic dossier on the cost effectiveness of siponimod (Mayzent®). 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 Applicant 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 **February 2021**

Summary

In May 2020, Novartis Ltd submitted an economic dossier on the cost effectiveness of siponimod (Mayzent®) for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity. Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator and reduces the recirculation of T cells into the central nervous system thereby limiting central inflammation. The standard maintenance dose of siponimod is 2mg once daily taken orally after an initial 5-day titration phase. Siponimod is metabolized in the liver through the Cytochrome P450 system. A genotype test of Cytochrome P450 2C9 (CYP2C9) is required prior to the initiation of therapy. The recommended maintenance dose is 1 mg once daily in patients with a CYP2C9*2*3 or a CYP2C9*1*3 genotype (approximately 15% of patients). Patients with a CYP2C9*3*3 genotype (1% to 2% of patients) should not be treated with siponimod as elevated drug levels will occur. Regulatory approval from the EMA was granted on the 20 January 2020. Reimbursement is sought under the High-Tech Drugs Arrangement.

Disease modifying therapies (DMTs) are targeted towards reducing the inflammatory aspects of multiple sclerosis (MS). There is no agreed standard of care DMT in Ireland for patients with active SPMS. Interferon-β-1b (Betaferon ®) is the only licensed DMT for active SPMS. Alternatively, patients may be prescribed other DMTs which are not licensed for SPMS but are licensed in relapsing or relapsing remitting MS. These include interferon-β-1a, teriflunomide, alemtuzumab, natalizumab, ocrelizumab, fingolimod, glatiramer acetate, dimethyl fumarate, and cladribine. Rituximab is not licensed for use in MS however it is used off license in SPMS. All are considered to be relevant comparators with siponimod in SPMS. Best supportive care (including anti-spasmodics, analgesics, anticholinergics) is also a relevant comparator for patients who are not receiving a DMT.

1. Comparative effectiveness of siponimod

The EXPAND trial was a double-blind, randomised, placebo-controlled trial in adults with SPMS. The overall population comprised patients with active SPMS and non-active SPMS. The trial was designed to assess whether siponimod reduces disease progression as measured by 3-month confirmed disease progression (3-month CDP) compared to placebo; 6-month CDP was a key secondary endpoint. The time to onset of disability progression in patients treated

with siponimod was delayed compared to placebo (3-month CDP: hazard ratio [HR] 0.79; 95% CI 0.65 to 0.95; 6-month CDP HR 0.74; 95% CI 0.60 to 0.92). The clinical efficacy data supporting the authorisation of siponimod in patients with active SPMS was derived from a post hoc subgroup analysis of this trial. In the subgroup with active SPMS, time to onset of disability progression was delayed with siponimod (3-month CDP HR 0.69; 95% CI 0.53 to 0.91; 6-month CDP HR 0.63; 95% CI 0.47 to 0.86). There is no direct evidence versus any of the comparators of interest. The Applicant conducted indirect treatment comparisons (ITC) using Bucher ITC methods and Matching-Adjusted Indirect Comparison (MAIC) methods to derive indirect relative efficacy estimates. However, there are significant limitations associated with both of these methods due to the underlying data. All of the comparator trials (1998 -2004) included in the indirect comparisons excluded patients who had a history of interferon treatment. The time bias limits the usefulness of ITC outputs given that clinical practice has changed over time. The MAIC analysis compared trials which reported results for the overall population. It was assumed that the overall SPMS population is a proxy for the active SPMS population. This assumption was considered to be unrealistic as efficacy differed between these populations in the EXPAND trial. A further limitation of the MAIC was that not all potential treatment effect modifiers were accounted for. The Bucher ITC method included trials which reported results in a "relapsing SPMS" population; this was defined inconsistently between studies and not fully aligned with the active SPMS population of interest. Outputs from the MAIC were used to inform the Applicant's cost-effectiveness evaluation. The Review Group considers that the Bucher ITC approach is more appropriate than the MAIC and therefore results from this method were used in the NCPE adjusted base case analysis. This comparison showed no statistically significant difference between siponimod and interferon-β-1b 250 mcg on time to disease progression (3-month CDP HR vs Relative Risk 0.81; 95% CI 0.57 to 1.15). As the hazard ratios for time to CDP-3 were not reported in the European study, hazard ratios for time to CDP-3 were derived from EXPAND individual patient data after following patients for 33 months to facilitate a direct comparison to the relative risk for the proportion with CDP-3 at 33 months reported by the European Study. The assumption that hazard ratios and relative risk of disease progression are interchangeable only holds as a crude approximation over a short time frame and introduces substantial uncertainty in the ITC estimates. Bucher ITC results were also available for time to 3 month-CDP and 6 month-CDP versus interferon β-1a 22mcg and interferon β-1a 44mcg, respectively. Bucher ITC

comparisons between other relevant comparators in active SPMS were not possible. In the absence of robust evidence on comparative efficacy, the NCPE conducted an exploratory analysis in which the treatment effects of all DMTs on disability progression and relapses were assumed to be equivalent.

2. Safety of siponimod

In total, 1,645 patients (overall population) were included in the safety set from the EXPAND trial. This comprised all randomised patients with assigned treatment who took at least one dose of study medication. Adverse events (AEs) were more frequent in the siponimod arm than in the placebo arm (88.7% versus 81.5%). Serious AEs were also more frequent in the siponimod arm (17.9% versus 15.2%). In total 12.6% of patients in the siponimod arm and 11.2% in the placebo arm experienced grade 3-4 AE however no individual grade 3-4 AE was experienced in greater than 2% of patients. More patients discontinued the study drug permanently due to AEs in the siponimod group (7.6% versus 5.1%). AEs of special interest reported more frequently in the siponimod group were herpes zoster reactivations (2.2% versus 0.7%), lymphopenia (1.6% versus 0%), macular oedema (1.7% versus 0.2%), and increased liver transaminases (1.4% versus 0.6%).

3. Cost effectiveness of siponimod

A cohort based multi-state discrete-time Markov model with a lifetime horizon was used to estimate cost effectiveness. The base case comparator was interferon-β-1b (Betaferon®). The Applicant also provided scenario analyses to allow for comparison to the other relevant comparators. The model structure comprises 10 mutually exclusive health states which represent differing levels of SPMS disability status according to the Expanded Disability Status Scale (EDSS) scores 0 to 9 inclusive, and a single state for death. The main driver of the model is disability progression. A key uncertainty in the model was an assumption of sustained efficacy. This assumption was not sufficiently supported by evidence.

In the Applicant's base case analysis, siponimod compared with interferon-β-1b (Betaferon ®) in the overall SPMS population was associated with an incremental cost of €59,948 and an incremental QALY gain of 1.16 resulting in an incremental cost effectiveness ratio (ICER) of €50,916 per QALY. However, the Review Group does not consider this ICER to be plausible,

primarily due to the use of MAIC estimates from the overall SPMS population, the assumption of sustained efficacy while patients remain on treatment, and an assumption that treatment is discontinued at EDSS Health State 8. The NCPE-adjusted base case was informed by the Bucher ITC analysis of the active SPMS population. The Review Group also applied a treatment efficacy waning in the NCPE adjusted base case and assumed treatment discontinuation at EDSS Health State 7, among other changes. In the NCPE-adjusted base case, the ICER was €265,383 per QALY (incremental cost €63,831; incremental QALY 0.24), with a probability of being cost-effective of 0% at a payer-threshold of €45,000 per QALY. Scenario analyses versus other comparators generated highly uncertain cost effectiveness results, with very limited relevance for decision-making.

4. Budget impact of siponimod

The proposed price to wholesaler is €1,707 per 2mg x 28-tablet pack. There is no price difference between the 1mg and 2mg tablets. The total drug cost to the HSE per patient per year including rebates and pharmacy fees is €23,568. Based on the Applicant's estimate of the current eligible population and the proposed market uptake of siponimod (11% in year 1 rising to 53% in year 5), the projected gross cumulative budget impact over 5 years is €35.7 million. Clinical opinion obtained in Ireland by the Applicant suggests that some DMTs are more likely to be displaced by siponimod than others, however, the Review Group could not validate these assumptions. The resultant projected net cumulative budget impact is €20.3 million over 5 years. The Applicant estimates that the inclusion of cost offsets due to a reduction in infusion costs for comparator drugs would reduce the 5-year cumulative net budget impact to €19.3 million. There is some uncertainty around the budget impact estimates as the assumed projected uptake could not be validated.

A Patient Organisation Submission from MS Ireland has been received by the NCPE and will be provided to the HSE. This submission will form part of the data that the HSE considers.

5. Patient submission

A Patient Organisation Submission from MS Ireland has been received by the NCPE and will be provided to the HSE. This submission will form part of the data that the HSE considers.

6. Conclusion

The NCPE recommends that siponimod 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.