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MS Research Australia is writing to support the inclusion of siponimod (Mayzent) on the Pharmaceutical Benefits Scheme (PBS) for people with relapsing forms of MS.

As the largest national not-for-profit organisation dedicated to funding MS discoveries and coordinating MS research in Australia, we are proud to advocate on behalf of people affected by this disease. One area of particular importance to MS Research Australia and the MS community is the affordable availability of treatments that have been shown to be effective in clinical trials to reduce the impact of MS.

MS affects everyone differently and people also respond to treatments and their potential side effects differently. Life circumstances, such as family planning, career and travel, as well as other health conditions, can also greatly affect treatment options and decisions. Even geography can affect treatment choices with close access to hospitals and health professionals for treatment, administration and monitoring being a big consideration relating to some medications for people with MS living outside of major metropolitan areas.

Finding the right treatment option for every individual with MS is paramount as suboptimal treatment can lead to an increased symptom burden and irreversible accumulation of disability. This in turn leads to an increased burden on the healthcare system and a further reduction in the quality of life of patients and their families. MS costs the Australian community over $1.75 billion per year[1]. The impact of MS on quality of life can be equivalent to that experienced by people with terminal metastatic cancer, chronic kidney disease and severe heart disease[1].

Siponimod acts by targeting lymphocytes and retaining them in lymphoid tissues[2]. This retention prevents potentially auto-aggressive lymphocytes from moving into the central nervous system, the site of inflammation in MS, and contributing to the ongoing damage to myelin and nerves that can lead to progressive disability. Siponimod is an oral tablet that involves an initial 6 day titration followed by a maintenance dose of 1mg or 2mg daily. Therefore, this treatment regime provides a potentially convenient option for people with relapsing forms of MS, particularly to those whom are located rurally and face a geographical barrier.

Siponimod has been shown in clinical trials to be an effective treatment to significantly reduce new and active lesions, and annualised relapse rate in people with relapsing remitting MS. In the BOLD clinical trial, which involved 297 people with relapsing remitting MS, participants were given either 0.25mg, 0.5mg, 1.25mg, 2mg, 10mg siponimod or placebo[3]. All doses of siponimod resulted in a reduction in combined unique active lesions compared to placebo at 3 months; 35% reduction for 0.25mg siponimod, 50% reduction for 0.5mg siponimod, 66% reduction for 1.25mg siponimod, 72% reduction for 2mg siponimod and an 82% reduction for 10mg siponimod. At 3 months, the number of monthly new or newly enlarged T2 lesions compared to placebo was significantly reduced for 10mg

siponimod (74%), 2mg siponimod (72%) and 1.25mg siponimod (88%). At 6 months, the number of new or newly enlarged T2 lesions were significantly reduced for 10mg siponimod (84%) and 2mg siponimod (80%) compared to placebo. Similar results were seen for the number of monthly new gadolinium-enhancing T1 lesions and the number of monthly gadolinium-enhancing T1 lesions. There was also reduction in annualised relapse rate at 6 months for the 2mg siponimod group compared to the placebo group. An extension of this clinical trial to 24 months showed that low disease activity was sustained[4].

Siponimod has also been shown in clinical trials to be an effective treatment to significantly reduce the risk of disease progression. In the EXPAND trial, which involved 1,651 people with secondary progressive MS including those who still experienced relapses, people who were given siponimod were compared with those who were given a placebo tablet[5]. Participants of the clinical trial were treated for up to three years and their disability was tracked every three months. The trial showed that an initial titration of siponimod for 6 days followed by 2mg siponimod once daily as a maintenance dose resulted in a 21% reduction in the risk of disability progression ($p = 0.013$). More people who received siponimod rather than placebo were free from gadolinium enhancing lesions (67% vs 89%) and from new or enlarging T2 lesions (37% vs 57%). Furthermore, siponimod also significantly reduced the rate of brain atrophy compared to placebo over a 24 month period (-0.50% vs -0.65%, $p = 0.0002$).

Siponimod has been shown to be largely well-tolerated by people with MS. The most common adverse effects were dizziness, nasopharyngitis, lymphopenia, hypertension, elevated liver enzymes and cardiac abnormalities at treatment initiation, which are consistent with other MS treatments in this class [3,4,5]. Cardiac abnormalities were mitigated by treatment titration at initiation.

MS Research Australia supports affordable access to all proven treatment options to increase the opportunity for people with MS and their doctors to find effective therapies suited to their individual circumstances. Reducing disease progression will improve quality for people with MS and their loved ones, enabling their full participation in social and family life, and employment.

MS Research Australia appreciates the opportunity to make this submission and applauds the Committee for seeking the views of people with MS and the wider community as part of the process of considering new MS treatments for inclusion on the PBS.

1) Health Economic Impact of MS in Australia in 2017. https://msra.org.au/wp-content/uploads/2018/08/health-economic-impact-of-ms-in-australia-in-2017_ms-research-australia_web.pdf
2) The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. Gergely P, Nuesslein-Hildesheim B, Guerini D, Brinkmann V, Traebert M, Bruns C, Pan S, Gray NS, Hinterding K, Cooke NG, Groenewegen A, Vitaliti A, Sing T, Luttringer O, Yang J, Gardin A, Wang N, Crumb WJ Jr, Saltzman M, Rosenberg M, Wallström E. Br J Pharmacol. 2012 Nov: 167(5):1035-47 doi: 10.1111/j.1476-5381.2012.02061.x.

3) Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study. Selmaj K, Li DK, Hartung HP, Hemmer B, Kappos L, Freedman MS, Stüve O, Rieckmann P, Montalban X, Ziemssen T, Auberson LZ, Pohlmann H, Mercier F, Dahlke F, Wallström E. Lancet Neurol. 2013 Aug: 12(8):756-67. doi: 10.1016/S1474-4422(13)70102-9.
4) Safety and Efficacy of Siponimod (BAF312) in Patients With Relapsing-Remitting Multiple Sclerosis: Dose-Blinded, Randomized Extension of the Phase 2 BOLD Study. Kappos L, Li DK, Stüve O, Hartung HP, Freedman MS, Hemmer B, Rieckmann P, Montalban X, Ziemssen T, Hunter B, Arnould S, Wallström E, Selmaj K. JAMA Neurol. 2016 Sep 1:73(9): 1089-98 doi: 10.1001/jamaneurol.2016.1451.
5) Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. EXPAND Clinical Investigators. Lancet. 2018 Mar 31:391(10127):1263-1273. doi: 10.1016/S0140-6736(18)30475-6.