27th January 2022

PBAC Secretariat
MDP 952
Department of Health and Ageing
GPO Box 9848
Canberra ACT 2601

By email to: pbac@health.gov.au

Re: Submission of diroximel fumarate (Vumerity®) for RRMS to PBAC meeting March 2022

MS Australia is writing to the Pharmaceutical Benefits Advisory Committee (PBAC) to support the inclusion of diroximel fumarate on the Pharmaceutical Benefits Scheme (PBS) for people with multiple sclerosis (MS).

MS Australia is Australia's national MS not-for-profit organisation that empowers researchers to identify ways to treat, prevent and cure MS, seeks sustained and systemic policy change via advocacy, and acts as the champion for Australia's community of people affected by MS. MS Australia is the largest Australian not-for-profit organisation dedicated to funding, coordinating, educating and advocating for MS research as part of the worldwide effort to solve MS. MS Australia collaborates closely with our member organisations and various national and international bodies to help meet the needs of people affected by MS.

Declaration of interest

MS Australia is making this submission as we have an interest in the health and well-being of all people with MS. MS Australia is the national peak body for people living with MS in Australia. We work with governments at all levels, engaging on the issues that concern the lives of people living with MS, their families and carers, the community and the economy. We declare that we have in the past received funding support from pharmaceutical companies, including Biogen Inc, with an interest in MS in the form of grants for projects and support of our national MS Research scientific conference.

About MS

As the national peak body for people with MS we are proud to advocate on behalf of our state member organisations and the MS community. One area we are particularly passionate about

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is the provision of more affordable and accessible treatments that can improve the lives of people with MS.

There are currently more than 25,600 people living with MS across the country and over 7.6 million Australians know or have a loved one with this disease. MS can be particularly debilitating and has an unpredictable disease course. No two cases of MS are the same.

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. There is no one-size fits all treatment for people living with MS and to date, there is no known cure.

Relapsing-remitting form MS (RRMS) is characterised by partial or total recovery after attacks, also called exacerbations, relapses, or flares. It is the most common form of MS with about 75% of people with MS initially diagnosed with a relapsing-remitting course.

The challenges faced by people with MS can be significant and can have a devastating impact on their families and the wider community. Relapses, as part of the course of RRMS can cause short-term or long-term disability, resulting in the need for physical and/or psychological care and support, medical investigations, treatments and hospitalisation.

About diroximel fumarate (Vumerity®)

Diroximel fumarate is a next-generation oral drug used for treatment of RRMS and is in the same class of MS treatment as dimethyl fumarate (Tecfidera®). Upon entering the body, diroximel fumarate is converted to the active metabolite monomethyl fumarate (MMF); this, in turn, is thought to activate a pathway to reduce oxidative stress, which in turn slows damage to myelin and the underlying nerves [https://www.vumerity.com/content/dam/commercial/vumerity/pat/en_us/pdf/vumerity-prescribing-information.pdf]. Diroximel fumarate is an oral capsule taken twice daily. Therefore, this treatment regime provides a potentially convenient option for people with relapsing remitting MS, particularly to those who are located rurally and face a geographical barrier.

The American Food and Drug Administration (FDA) has approved the use of diroximel fumarate for the treatment of relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting MS (RRMS), and active secondary progressive MS (SPMS) in 2019 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211855s000lbl.pdf). Recently, the European Medicines Agency (EMA) approved the use of diroximel fumarate for the treatment of relapsing remitting MS.

Clinical trials

In the 96-week phase III clinical trial named EVOLVE-MS-1, the interim safety and efficacy of diroximel fumarate was investigated in 696 patients with RRMS[1]. By week 48, the mean number of gadolinium-enhancing lesions was significantly reduced from baseline by 77%, ($p<0.0001$) and by 96% ($p=0.0051$) in newly diagnosed patients. Additionally, a larger percentage of both populations had zero gadolinium-enhancing lesions at week 48 compared with baseline.

The adjusted annualised relapse rate (ARR) was low at 0.16%. This is similar to that observed with DMF in the ESTEEM trial (0.18)[2]. By week 48, 88.8% of the overall population had no

relapses, 9.5% had one relapse and 0.1% had four or more. Compared to the 12 months before the study, there was a 79.5% reduction in the ARR.

Diroximel fumarate has been shown to be largely well-tolerated by people with MS. Like dimethyl fumarate, there was a decline in lymphocytes over the first year of treatment followed by stabilisation. Gastrointestinal (GI) events are one of the most reported adverse events within the first 1-2 months of dimethyl fumarate treatment, which has led to treatment discontinuation in up to 20% patients[1]. The EVOLVE-MS-1 clinical trial reported lower than expected rates of GI events, with most GI events being mild to moderate, leading to a discontinuation in 0.7% patients at the time of publication.

In the phase III clinical trial named EVOLVE-MS-2, the GI tolerability was compared between dimethyl fumarate and diroximel fumarate over 5 weeks in patients with RRMS using two self-administered GI symptoms scales[3]. Patients in the diroximel fumarate arm experienced 46% less days with an Individual Gastrointestinal Symptom and Impact Scale (IGISIS) symptom intensity score of >2 compared to patients in the dimethyl fumarate arm. There were also lower rates of GI adverse events observed with diroximel fumarate than dimethyl fumarate (34.8% vs. 49.0%). Furthermore, fewer patients discontinued diroximel fumarate than dimethyl fumarate due to adverse events (1.6% vs. 5.6%) and GI adverse events (0.8% vs. 4.8%).

Impact of new MS medications

Being able to better manage and limit the frequency and impact of relapses, reduce the number of new lesions and experience less worsening of disability, can help alleviate the burden of MS on the community and the individual.

A key distinction is that **diroximel fumarate** can be taken at home rather than requiring injection or hospital infusion. Therefore, this treatment regime provides a potentially convenient option for people with relapsing MS, particularly for those located remotely.

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 with an average cost of MS per person of $68,382 (similar to that of someone with Parkinson's disease or the first year after a stroke, triple that of a person with type 2 diabetes)[4]. 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].

In addition, this study reported that on average, the quality of life of people with MS in Australia is 31% less than that of the overall Australian population. Quality of life for people with MS who are living with severe disability is 41% lower compared to people with MS with no disability. This substantially reduced quality of life is primarily driven by the impact of MS on pain, independent living, mental health and relationships.

Including this medication on the PBS will make a valuable addition to the repertoire of medications available to people with MS and their neurologists. It will allow for an additional appropriate treatment choice to be made according to the efficacy and possible side-effects in relation to an individual's circumstances and will help to improve the quality of life and alleviate the economic cost of MS to individuals, their families and the broader community.

We appreciate you considering this treatment for inclusion on the PBS.

1. Naismith, R. T. *et al.* Diroximel fumarate (DRF) in patients with relapsing–remitting multiple sclerosis: Interim safety and efficacy results from the phase 3 EVOLVE-MS-1 study. *Mult. Scler. J.* **26**, 1729–1739 (2020).
2. Giles, K. *et al.* Efficacy of Delayed-Release Dimethyl Fumarate in Newly Diagnosed and Other Early Multiple Sclerosis Patients, and Patients Switching from Interferon or Glatiramer Acetate, in Routine Medical Practice: Interim Results from ESTEEM (P1.367). *Neurology* **90**, (2018).
3. The EVOLVE-MS-2 Study Group *et al.* Diroximel Fumarate Demonstrates an Improved Gastrointestinal Tolerability Profile Compared with Dimethyl Fumarate in Patients with Relapsing–Remitting Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III EVOLVE-MS-2 Study. *CNS Drugs* **34**, 185–196 (2020).
4. *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.