5.06 DIROXIMEL FUMARATE, Capsule 231 mg, Vumerity®, Biogen Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule, Authority Required (STREAMLINED) listing for diroximel fumarate (DRF) for treatment of relapsing-remitting multiple sclerosis (RRMS). This is the first submission for DRF in RRMS.

1.2 Listing was requested on the basis of a cost-minimisation analysis to dimethyl fumarate (DMF) which is bioequivalent in the active metabolite, monomethyl fumarate (MMF). The submission nominated DMF as the sole comparator for DRF on the basis that DMF is a pharmacological analogue of DRF.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Relapsing-remitting multiple sclerosis (RRMS)
Intervention	Diroximel fumarate (DRF) 2 x 231 mg capsules BID (maintenance dose = 924 mg daily)
Comparator	Dimethyl fumarate (DMF) 240 mg capsules BID (maintenance dose = 480 mg daily)
Outcomes	• Number of days with any IGISIS Symptom Intensity Score ≥2 relative to exposure days • Summary of number of days with a IGISIS or GGISIS Symptom Intensity Score • Worst IGISIS Individual Symptom Intensity Score by Week • Interference, bothersomeness and impact on work • Other safety outcomes (TEAEs and SAEs) • Exploratory efficacy outcomes: - ARR - GD+ lesions • Number of new/newly enlarging T2 lesions
Clinical claim	In patients with RRMS, DRF is non-inferior in effectiveness (since DRF and DMF are bioequivalent in terms of therapeutic doses of active metabolite)[a] and non-inferior in terms of safety (GI tolerability [IGISIS & GGISIS scores], discontinuations and AEs) compared with DMF.

Source: Table 1.1.1, p30 of the Submission.

AE, adverse events; ARR, annualised relapse rate; BID, twice daily; DMF, dimethyl fumarate; DRF, diroximel fumarate; GD+, gadolinium positive, GGISIS, Global Gastrointestinal Symptom and Impact Scale; GI, gastrointestinal; IGISIS, Individual Gastrointestinal Symptom and Impact Scale; mg, milligram; RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event; TEAE, treatment-emergent adverse events

a. Dimethyl fumarate (DMF) was recommended for listing on the PBS in July 2013 on a cost-minimisation basis with ABCR therapies (intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b and glatiramer acetate; DMF Public Summary Document (PSD), July 2013 p.6-7).

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. The Delegate's Overview and ACM advice were available at time of PBAC consideration, both of which supported the registration of DRF.

3 Requested listing

3.1 The requested restriction is presented below. A grandfathering restriction was requested in the Pre-PBAC Response, which has been added to the requested listing.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer	
DIROXIMEL FUMARATE Capsule 231 mg, 120	NEW	1	120	5	Vumerity®	Biogen Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☒Authority Required - Streamlined
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Condition: Multiple sclerosis
Indication: Multiple sclerosis
Treatment Phase: Initial treatment
Clinical criteria:
The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised disease modifying therapy for this condition.
AND
Clinical criteria:
Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy for this condition.

AND
Clinical criteria:
Patient must be ambulatory (without assistance or support)
AND
Prescribing Instructions: Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.

Treatment Phase: Continuing treatment
Clinical criteria:
The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised disease modifying therapy for this condition.
AND
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not show continuing progression of disability while on treatment with this drug
Prescribing Instructions: Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.

Treatment Phase: Grandfather treatment
Clinical criteria:
Patient must have commenced non-PBS-subsidised treatment with this drug for this PBS indication prior to <<PBS list date>>
AND
Clinical criteria:
The condition must be/have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of at least one of the brain/spinal cord; OR The condition must be/have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis supported by written certification, which is documented in the patient's medical records, from a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient.
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised disease modifying therapy for this condition.
AND
Clinical criteria:
Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
AND
Clinical criteria:
Patient must be ambulatory (without assistance or support)
Prescribing Instructions: Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.

3.2 A Special Pricing Arrangement (SPA) was requested for listing DRF, similar to the arrangement currently in place for DMF.

3.3 The requested restriction is consistent with the proposed TGA indication and is consistent with current PBS listings for RRMS disease modifying therapies (DMTs).

3.4 In its Pre-PBAC Response , the Sponsor requested the addition of a grandfather restriction for a planned product familiarisation program, set to commence |||

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Multiple sclerosis (MS) is characterised by the development of inflammatory plaques in the Central Nervous System including the brain, spinal cord and optic nerves. In MS, T lymphocytes play a role in destroying myelin, the protective sheath that surrounds nerve fibres and helps with the efficient flow of nerve signals to and from the brain and various parts of the body. In people with MS, there is inflammation around the Th1 and Th17 lymphocytes (which are associated with inflammatory cytokines that activate macrophages and opsonising antibodies). Areas of damaged myelin become scarred and can no longer fully insulate the nerve, leaving unprotected areas, where the flow of nerve impulses is interrupted. This interruption in the communication between the brain and other parts of the body results in MS symptoms.

4.2 MS may manifest in relapsing and progressive forms. RRMS is the most common disease course, estimated in 85% of initial diagnoses, and is characterised by clearly defined attacks of new or increasing neurologic symptoms. These attacks (relapses or exacerbations) are followed by periods of partial or complete recovery (remissions). During remissions, all symptoms may disappear, or some symptoms may continue and become permanent. There is no apparent progression of the disease during the periods of remission.

4.3 Symptoms of MS can manifest in many different ways, depending on where lesions develop on the brain and spinal cord. Symptoms are episodic, often with gradual onset, acute stages or progressive decline of function. They differ from person to person and can require constant adaptation, transitioning and adjustments, especially given the symptoms may interact (triangulate) with other symptoms (or comorbidities) and therefore cannot be assessed in isolation. Symptoms can also be invisible (such as increased brain atrophy), debilitating and result in a range of functional impairments.

4.4 The submission noted that all PBS listed DMTs are available as a first line treatment option and it is up to prescribing physicians to determine the course of treatment for patients. While the course of treatment is often determined by disease progression, it is acknowledged that some patients may switch from one treatment to another due to compliance issues, patient preference, pregnancy status and adverse events. As per

the current PBS' RRMS listing for DMF, the condition must be diagnosed as clinically definite RRMS by MRI of the brain and/or spinal cord with at least two documented relapses within the previous two years. Under the proposed PBS listing, the positioning of DRF would be as an alternative DMT, similar to DMF, and therefore not change the current treatment algorithm.

4.5 DRF belongs to the therapeutic class of L04AX (Antineoplastic and immunomodulating agents, other immunosuppressant). Following oral administration, DRF is metabolised to the primary active metabolite MMF, major inactive metabolite 2-hydroxyethyl succinimide (HES) and the minor inactive metabolites RDC-8439 and methanol, similar to the metabolic pathway for DMF. The metabolism of DRF and DMF produce equivalent quantities of the active metabolite (MMF). The primary active metabolite MMF significantly reduces immune cell activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli and also affects lymphocyte phenotypes through a down-regulation of pro-inflammatory cytokine profiles (Th1, Th17) and biases towards anti-inflammatory Th2 production (Dimethyl fumarate Australian Public Assessment Record, TGA 2013). The metabolism of DRF creates smaller amounts of free methanol than that of DMF.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated DMF as the main comparator. The main arguments provided in support of this nomination were that DRF is a pharmacological analogue of DMF, which is currently listed on the PBS. At therapeutic doses, DRF and DMF produce bioequivalent systemic exposure of MMF which is thought to drive efficacy in patients with MS. Based on the active metabolite (MMF) being the same, DMF was an appropriate comparator.

5.2 For the requested RRMS population, all PBS-listed RRMS medicines may be considered alternative therapies for DRF and DMF because they could be replaced in practice. However, given the established therapeutic relativities have resulted in two 'efficacy tiers' in RRMS, the following therapies which are in the same tier as DMF (the 'lower efficacy' tier) are likely to be the most relevant: the ABCR drugs (interferon beta-1a and 1b, glatiramer acetate), peginterferon beta-1a and teriflunomide.

5.3 The PBAC has previously considered that:

- The ABCR therapies are equivalent to each other based on a series of non-inferiority comparisons.
- DMF is non-inferior in effectiveness and safety to the ABCR therapies based on a direct comparison with glatiramer acetate and a series of indirect comparisons with interferon beta-1a and 1b, using placebo common comparator (Public Summary Document (PSD) July 2013).

- Teriflunomide is non-inferior in efficacy and has a different but non-inferior safety profile to interferon beta-1a and 1b based on a series of direct, indirect and post-hoc comparisons (PSD July 2013).
- Peginterferon beta-1a is non-inferior in efficacy and safety to interferon beta-1a, based on an indirect comparison using placebo as common comparator (PSD November 2014).

5.4 Other PBS-listed DMTs for RRMS patients include: natalizumab, fingolimod, alemtuzumab, ocrelizumab, cladribine, ozanimod, ofatumumab and siponimod. These drugs are available for RRMS first line treatment, and also as second- and third-line therapies. These agents are in the 'higher efficacy' tier of DMTs for RRMS and whilst they may be replaced in practice, the PBAC has previously considered these medicines provide a significant improvement in efficacy compared with the 'lower efficacy' tier of medicines.

5.5 A consideration of the PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the Committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy or reduction in toxicity over the alternative therapy(ies), and if satisfied, must make a statement to that effect. The relevant alternative therapies are: interferon beta-1a (intramuscular or subcutaneous forms), interferon beta-1b, peginterferon beta-1a, glatiramer acetate, teriflunomide and DMF.

5.6 The Pre-Sub-Committee response (PSCR) argued teriflunomide is not a relevant alternative, as teriflunomide is a pregnancy Category X drug and noted additional safety concerns with teriflunomide, including a black box safety warning applied by the US FDA due to hepatotoxicity concerns. The ESC considered that a substantial proportion of the RRMS population is of childbearing age and would generally not be treated with teriflunomide.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (6) and MS Australia via the Consumer Comments facility on the PBS website. The comments described the benefits to patients of an alternative to DMF which offered the same level of effectiveness with fewer gastrointestinal side effects, a known issue associated with DMF treatment which impacts quality of life for patients.

Clinical trials

6.3 The submission was based on one head-to-head randomised trial (EVOLVE-MS-2, N=506) comparing tolerability of DRF to DMF, and three Phase 1 clinical trials (ALK8700-A103, N=35; ALK8700-A104, N=42; ALK8700-A109, N=48) assessing relative bioavailability of DRF compared to DMF. Details of the trials presented in the submission are provided in Table 1 below.

6.4 The submission also provided supporting evidence for clinical safety from the EVOLVE-MS-1 (an ongoing, open-label, 96-week, single arm trial of DRF assessing safety, tolerability, and efficacy in RRMS patients) and an indirect comparison of DRF and DMF based on propensity score matched analysis of EVOLVE-MS-1 (DRF arm) and DEFINE/CONFIRM (DMF arm).

Table 2: Trials and associated reports presented in the Submission

Trial ID	Protocol title/ Publication title	Publication citation
ALK8700-A103	A Phase 1 Study to Determine the Relative Bioavailability of Monomethyl Fumarate Following Administration of ALKS 8700 and Dimethyl Fumarate in Healthy Subjects. Alkermes Clinical Study Report. Wehr, A., Hard, M., Yu, M., et al. "Relative Bioavailability of Monomethyl Fumarate after Administration of ALKS 8700 and Dimethyl Fumarate in Healthy Subjects."	30 January 2018 Neurology. 2018; 90(15)
ALK8700-A104	A Phase 1 Study To Assess The Comparative Bioavailability of Monomethyl Fumarate Following Administration of ALKS 8700 and Dimethyl Fumarate in Healthy Subjects Under Fed Conditions Alkermes Clinical Study Report	13 May 2016
ALK8700-A109	A Phase 1 Study to Assess the Comparative Bioavailability, Safety and Tolerability of Monomethyl Fumarate Following Administration of ALKS 8700 and Dimethyl Fumarate in Healthy Subjects When Taken with Meals of Varying Fat and Caloric Content. Alkermes Clinical Study Report.	2 June 2017
EVOLVE-MS2	A Phase 3 Study in Subjects with Relapsing-Remitting Multiple Sclerosis to Evaluate the Tolerability of ALKS 8700 and Dimethyl FumarateAlkermes Clinical Study Report	19 November 2019

Trial ID	Protocol title/ Publication title	Publication citation
	Naismith, R. T., Wundes, A., Ziemssen, T., 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. 2020; 34(2): 185-196
	Wundes, A., Wray, S., Gold, R., et al. "Improved gastrointestinal profile with diroximel fumarate is associated with a positive impact on quality of life compared with dimethyl fumarate: results from the randomized, double-blind, phase III EVOLVE-MS-2 study."	Therapeutic Advances in Neurological Disorders. 2021; 14.
	Naismith, R. T., Leigh-Pemberton, R. A., Rezendes, D., et al. "EVOLVE-MS-2: A randomized, double-blind, phase 3 study of the gastrointestinal tolerability of ALKS 8700 versus dimethyl fumarate in relapsing-remitting multiple sclerosis."	Multiple Sclerosis Journal. 2017; 23(3): 345-346.
	Naismith, R. T., Wolinsky, J. S., Jasinska, E., et al. "Interference of GI symptoms with daily activities and work productivity in MS patients treated with diroximel fumarate versus dimethyl fumarate."	Multiple Sclerosis Journal. 2020; 26(1 SUPPL): 138-139
	Wundes, A., Wolinsky, J. S., Wray, S., et al. "Improved gastrointestinal tolerability profile with diroximel fumarate compared to dimethyl fumarate in relapsing ms patients."	Neurology. 2020; 94(15).
	Wundes, A., Wray, S., Jasinska, E., et al. "Improved gi tolerability with diroximel fumarate is associated with clinically meaningful benefits on qol compared to dimethyl fumarate in evolve-MS-2."	Multiple Sclerosis Journal. 2020; 26(3 SUPPL): 221-222
Supportive data EVOLVE-MS-1 and DEFINE/CONFIRM	Wu, F., Gold, R., Freedman, M. S., et al. "Efficacy outcomes for diroximel fumarate compared with dimethyl fumarate: A propensity score matched analysis of EVOLVE-MS-1 and DEFINE/CONFIRM."	European Journal of Neurology. 2019; 26: 680-681.
EVOLVE-MS-1	A Phase 3 Open Label Study to Evaluate the Long-term Safety and Tolerability of ALKS 8700 in Adults with Relapsing Remitting Multiple Sclerosis Biogen Clinical Study Report	4 March 2021
	Wray S, Singer BA, Drulovic J, Chen H, Hanna J, Lyons J, Bergh FT, Kapadia S, Negroski D.I. Interim Safety and Efficacy Outcomes in Patients With Relapsing-Remitting Multiple Sclerosis who Received Diroximel Fumarate for Up to 2 Years.	*Neurology. 2020; 96(15).*

Source: Table 2.2.2, pp62-63 of the submission.

6.5 The key features of the clinical trials are summarised in the Table 2.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Bioequivalence studies						
ALK8700-A103	35	R, DB 15 days	Low	Healthy	PK, safety	NA
ALK8700-A104	42	R, DB 10 (+2) days	Low	Healthy	PK, safety	NA
ALK8700-A109	48	R, OL 20 days	High	Healthy	PK, safety	NA
RCT						
EVOLVE-MS-2	506	R, DB 5 weeks	Low	RRMS	IGIS intensity score; GGISIS symptom intensity; interference, bothersomeness and impact on work; safety	NA

Source: pp66-71,85-89,95-96 of the submission.
DB, double blind; GGISIS, Global GI Symptom and Impact Scale; GI, gastrointestinal; IGISIS, Individual GI Symptom and Impact Scale; NA, not applicable; OL, open-label; R, randomised; RRMS, relapsing-remitting multiple sclerosis;

6.6 ALK8700-A109 was identified as having a high risk of bias due to it being an open-label study, increasing the likelihood of performance bias. In an independent quality assessment of the three bioequivalence studies, the method of random sequence generation and method for allocation concealment was not clear with a resulting uncertain risk of bias. The TGA Round 1 CER noted that while the EVOLVE-MS-2 trial met its primary endpoints, the deviation from protocol potentially introduced bias and confounding to the study, thus adversely impacting the generalisability of the study results. The protocol amendments included changes in primary, secondary and exploratory endpoints, and sample size to maintain study power, and choice of a pooled analysis in the primary endpoint.

Comparative effectiveness

6.7 Table 3 shows the analysis of covariance (ANCOVA) results for DRF and DMF administration for studies ALK8700-A103 and ALK8700-A104.

6.8 In Study ALK8700-A103, across all 3 parameters (AUClast, AUC∞, and Cmax), the geometric mean ratios were close to 1, and the 90% confidence intervals (CIs) were contained completely within the standard boundaries of 0.8 to 1.25 used to evaluate bioequivalence.

6.9 In Study ALK8700-A104, for MMF AUClast and AUC∞ the geometric mean ratios were close to 1 and the 90% CIs were contained completely within the standard boundaries of 0.8 to 1.25 used to evaluate bioequivalence. However, MMF mean Cmax was 26% lower for DRF as compared with DMF under fed conditions. The Submission argued that the presence of multiple peaks along with highly variable Cmax due to the intake of food likely explains this difference and that the similarity in tmax and tlag between the two treatments suggests a comparable rate of absorption.

Table 4: Summary of ANCOVA results for plasma MMF AUC0-last, AUC0-∞, and Cmax following a single oral administration of 462 mg DRF (Test) versus 240 mg DMF (Reference) formulations, PK Population - ALK8700-A103 and ALK8700-A104

PK parameter[a]	Geometric mean (SE)		Geometric mean ratios	90% CI of the geometric mean ratios
	DRF	DMF		
Study ALK8700-A103				
$AUC_{0\text{-last}}$ (h•µg/mL)	3.38 (0.05) n=35	3.14 (0.05) n=35	1.08	(1.00, 1.16)
$AUC_{0\text{-}\infty}$ (h•µg/mL)	3.57 (0.06) n=22	3.56 (0.07) n=14	1.00	(0.88, 1.14)
C_{max} (µg/mL)	1.57 (0.07) n=35	1.67 (0.07) n=35	0.94	(0.82, 1.07)
Study ALK8700-A104				
$AUC_{0\text{-last}}$ (h•µg/mL)	2.69 (0.04) n=42	2.80 (0.04) n=42	0.96	(0.89, 1.03)
$AUC_{0\text{-}\infty}$ (h•µg/mL)	2.83 (0.05) n=25	3.08 (0.05) n=25	0.92	(0.84, 1.01)
C_{max} (µg/mL)	0.88 (0.08) n=42	1.18 (0.08) n=42	0.74	(0.64, 0.85)

Source: Table 2.5.1, p 79 of the Submission. CSR ALK8700-A103, Table 7 p47; CSR ALK8700-A104, Table 9 p43;
ANCOVA, analysis of covariance; AUC∞, area under the concentration-time curve from time zero to infinity; AUC0-last, area under the curve from time zero until the last measurable concentration time point; CI, confidence interval; Cmax, maximum plasma concentration; DMF, dimethyl fumarate; DRF, diroximel fumarate; MMF, monomethyl fumarate; n, number of subjects included in the calculation of the geometric LSM and SE, which is the number of subjects with specific PK data while on any of the dose regimens; PK, pharmacokinetic; SE, standard error; µg, microgram.
Note: The SE displayed is in logarithmic scale.
[a] Based on an analysis of variance model, including treatment sequence, treatment group, and period as fixed factors and subject within treatment sequence as a random factor.

6.10 A summary of the bioavailability results from Study ALK8700-A109 for MMF after DMF following a high fat/high calorie meal or DRF under medium or low-fat administration relative to DMF administration under fasted conditions are shown in Table 4. Following administration of DMF with a high fat/high calorie meal, MMF Cmax, AUClast, and AUC∞ decreased by 41%, 18%, and 3%, respectively. Following administration of DRF with a medium fat/medium calorie meal, MMF Cmax, AUClast, and AUC∞ decreased by 27%, 7%, and 4%, respectively. Following administration of DRF with a low fat/low calorie meal, MMF Cmax, AUClast, and AUC∞ decreased by 15%, 4%, and 2%, respectively.

Table 5: Summary of mixed effects model for plasma MMF AUClast, AUC∞ and Cmax following a single oral administration of DMF 240 mg (Test) or DRF 462mg (Test) versus DMF 240 mg (Reference) – PK Population- ALK8700-A109

PK parameter[a]	Geometric Mean (SE)		Geometric Mean Ratios	90% CI of the Geometric Mean Ratios
	DRF N=48	DMF N=48		
DMF 240 mg with High Fat/High Calorie Meal (Test) versus DMF 240 mg Fasted (Reference)				
C_{max} (µg/mL)	0.96 (0.08) n=47	1.62 (0.08) n=48	0.59	(0.50, 0.71)
$AUC_{0\text{-last}}$ (h•µg/mL)	2.37 (0.08) n=47	2.91 (0.08) n=48	0.82	(0.69, 0.97)
$AUC_{0\text{-}\infty}$ (h•µg/mL)	2.82 (0.07) n=23	2.91 (0.05) n=43	0.97	(0.86, 1.09)
DRF 462 mg with Medium Fat/Medium Calorie Meal (Test) vs DMF 240 mg Fasted (Reference)				
C_{max} (µg/mL)	1.18 (0.07) n=47	1.62 (0.07) n=48	0.73	(0.62, 0.86)
$AUC_{0\text{-last}}$ (h•µg/mL)	2.70 (0.05) n=47	2.91 (0.05) n=48	0.93	(0.84, 1.02)
$AUC_{0\text{-}\infty}$ (h•µg/mL)	2.82 (0.05) n=33	2.92 (0.05) n=43	0.96	(0.88, 1.05)
DRF 462 mg with Low Fat/Low Calorie Meal (Test) vs DMF 240 mg Fasted (Reference)				
C_{max} (µg/mL)	1.38 (0.06) n=47	1.62 (0.06) n=48	0.85	(0.74, 0.98)
$AUC_{0\text{-last}}$ (h•µg/mL)	2.80 (0.05) n=47	2.91 (0.05) n=48	0.96	(0.88, 1.06)
$AUC_{0\text{-}\infty}$ (h•µg/mL)	2.89 (0.05) n=41	2.93 (0.05) n=43	0.98	(0.89, 1.09)

Source: Table 2.5.2, p80 of the Submission. CSR ALK8700-A109, Table 12 p49; Table 13 p50; Table 14 p51.
AUC∞, area under the concentration-time curve from time zero to infinity; AUC0-last, area under the curve from time zero until the last measurable concentration time point; CI, confidence interval; Cmax, maximum plasma concentration; DMF, dimethyl fumarate; DRF, diroximel fumarate; MMF, monomethyl fumarate; N, number of subjects who received a specific treatment; subjects could be included in more than 1 treatment group; n, number of subjects included in the calculation of the geometric LSM and SE, which is the number of subjects with specific PK data while on any of the dose regimens; PK, pharmacokinetic; SE, standard error
Note: The SE displayed is in logarithmic scale.
Geometric mean and geometric mean ratio are obtained from back transformation of the least square mean and least square mean difference in the log scale.
[a] Based on a mixed effects model, including treatment sequence, treatment group, and period as fixed factors and subject within treatment sequence as a random factor.

6.11 The TGA Round 1 CER considered that MMF exposure appeared to be bioequivalent between DRF and DMF at commercial doses (p64 of CER).

Supplementary efficacy evidence

6.12 The submission also presented the results of a conference abstract by Wu et al. 2019 that was identified in the literature search which compared efficacy outcomes for DRF compared with DMF using a propensity score matched analysis.

6.13 The results of the propensity score matching are summarised in Table 6. The results do not show a significant difference in clinical outcomes between DRF and DMF, however, this is an indirect comparison with the following issues:

- The primary outcomes of these trials (EVOLVE-MS-1, CONFIRM, DEFINE) are different from each other, and therefore, it is uncertain that that these studies are powered to detect differences in outcomes.
- The submission did not discuss the methods used for indirect comparison of clinical outcomes or choice of clinical outcomes. Insufficient details of the DEFINE and CONFIRM studies was provided in the submission to assess the similarity between the studies apart from baseline characteristics.

Table 6: Results of PSM at Week 48 (EVOLVE-MS-1, CONFIRM and DEFINE trials)

Category	DRF	DMF	Results
Gd+ lesions, mean (SD)	0.2 (0.8)	0.3 (1.2)	Odds Ratio: 0.983 (95% CI: 0.546-1.772) P-value: 0.955
Adjusted mean number of new/newly enlarging T2 lesions	1.941	1.726	Mean ratio: 1.124 (95% CI: 0.863-1.464) P-value: 0.384
ARR (95% CI)	0.169 0.109-0.261 0.109-0.261 (0.109-0.261)	0.206 0.109-0.261 0.109-0.261 (0.135-0.316)	ARR ratio: 0.819 (95% CI: 0.580-1.155) P-value: 0.255

Source: Table 2.9.2, p112 of the Submission.
ARR, adjusted annualised relapse rate; CI, confidence interval; DMF, dimethyl fumarate; DRF, diroximel fumarate; SD, standard deviation; Gd+, Gadolinium-enhancing

Comparative harms

6.14 The submission presented the safety evidence in relation to gastrointestinal (GI) tolerability from the EVOLVE-MS-2 trial. For the number of days with any IGISIS individual symptom intensity score ≥ 2 relative to exposure days in Parts A [exploratory] and B, the adjusted rate ratio RR (95% CI) was calculated as 0.54 (0.39-0.75), favouring DRF over DMF treatment (p = 0.0003). Four other secondary endpoints (out of seven) relating to GI symptoms also showed a statically significant reduction in the DRF group compared to the DMF group. The Global Gastrointestinal Symptom and Impact Scale (GGISIS) and Individual Gastrointestinal Symptom and Impact Scale (IGISIS) were exploratory measurement tools and have not been validated or used in previous clinical trials (TGA Round 1 CER, p48).

6.15 Table 5 presents a summary of adverse events (AE) in the included randomised trials, including the bioequivalence studies and EVOLVE-MS-2. No serious AEs or AEs leading to treatment discontinuation were observed in ALK8700-A103, ALK8700-A104 or ALK8700-A109 and these outcomes are not reported in the table below for brevity reasons.

Table 7: Summary of key adverse events in the trials

Trial ID	DRF n with event/N (%)	DMF n with event/N (%)	RR (95% CI)
ALK8700-A103			
Any TEAE	16/35 (45.7)	19/35 (54.3)	0.84 (0.37, 1.31)
TEAE by highest severity Mild Moderate Severe	 16/35 (45.7) 0 0	 18/35 (51.4) 1/35 (2.9) 0	 0.89 (0.41, 1.37) - -
Drug-related TEAE[a]	15/35 (42.9)	19/35 (54.3)	0.79 (0.30, 1.28)
ALK8700-A104			
Any TEAE	13/42 (31.0)	14/42 (33.3)	0.93 (0.31, 1.55)
TEAE by highest severity Mild Moderate Severe	 13/42 (31.0) 0 0	 14/42 (33.3) 0 0	 0.93 (0.31, 1.55)
Drug-related TEAE[a]	11/42 (26.2)	13/42 (31.0)	0.85 (0.17, 1.53)
ALK8700-A109			
Any TEAE	Fed (low fat/calorie) 16/48 (33.3) Fed (medium fat/calorie) 20/48 (41.7)	Fasted 27/48 (56.3) Fed (high fat/calorie) 13/48 (27.1)	-
TEAE by highest severity			
Mild *(No moderate or severe TEAEs reported)*	Fed (low fat/calorie) 16/48 (33.3) Fed (medium fat/calorie) 20/48 (41.7)	Fasted 27/48 (56.3) Fed (high fat/calorie) 13/48 (27.1)	-
Drug-related TEAE[a]	Fed (low fat/calorie) 16/48 (33.3) Fed (medium fat/calorie) 20/48 (41.7)	Fasted 25/48 (52.1) Fed (high fat/calorie) 11/48 (22.9)	-
EVOLVE-MS-2			
At least one AE, n (%)	198 (78)	210 (84)	0.94 (0.86, 1.02)
AE by severity, n (%) Mild: Grade 1 AE Moderate: Grade 2 AE Severe: Grade 3 AE	 125 (49) 68 (27) 5 (2)	 121 (48) 75 (30) 14 (6)	 1.02 (0.86, 1.23) 0.90 (0.68, 1.19) **0.35 (0.13, 0.97)**
AE related, n (%)	165 (65)	181 (72)	0.90 (0.80, 1.02)
AE leading to discontinuation of study medication, n (%)	4 (2)	15 (6)	**0.26 (0.09, 0.79)**
GI AEs leading to study discontinuation, n (%)	2 (1)	12 (5)	**0.17 (0.04, 0.73)**
At least one SAE, n (%)	4 (2)	3 (1)	1.32 (0.30, 5.85)
SAE by severity, n (%) Mild: Grade 1 Moderate: Grade 2 Severe: Grade 3	 0 3 (1) 1 (0)	 1 (0) 1 (0) 1 (0)	 - 2.98 (0.31, 28.42) 0.99 (0.06, 15.77)
SAE related, n (%)	0	0	-
SAE leading to death, n (%)	0	0	-

Source: Table 2.5.3, p83 and Table 2.86 p106 of the Submission. CSR ALK8700-A103, Table 8 p49; CSR ALK8700-A104 Table 10 p45; CSR ALK8700-A109 Table 15 p55

AE, adverse event; CI = confidence interval; DMF, dimethyl fumarate; DRF, diroximel fumarate; n, number of participants reporting data; N, total participants in group; RD, risk difference; RR, relative risk; SAE, serious adverse event; TEAE, treatment emergent adverse event

Notes: [a] Related includes definitely related, probably related, or possibly related

6.16 In EVOLVE-MS-2 a nominally statistically significantly lower proportion of patients treated with DRF reported severe Grade 3 AEs, or AEs (including GI-related AEs) leading to discontinuation of study medication.

6.17 The TGA Round 1 CER reported that the safety profile of DRF is expected to be essentially the same as DMF, based on the results from bioequivalence studies (TGA Round 1 CRE, p64).

Clinical claim

6.18 The submission described DRF as non-inferior in terms of efficacy compared to DMF. This claim was adequately supported given the bioavailability of the active metabolite (MMF) presented in the comparative pharmacokinetic (PK) trials.

6.19 The submission described DRF as non-inferior in terms of safety compared to DMF, based on the evidence of adverse events reported in the trials. The submission also claimed that DRF has an improved overall safety profile compared to DMF, particularly with respect to GI tolerability. The claim might not be well supported due to the potential bias in the EVOLVE-MS-2 trial.

6.20 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.21 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.22 The submission presented a cost-minimisation analysis of DRF compared to DMF, based on the continuing treatment doses. The initial phase (7 days for both drugs, half of the maintenance dose) was not considered in the calculation.

6.23 The equi-effective dose for continuing treatment was estimated as:

- DRF 924 mg daily (2 x 231 mg capsules BID) = DMF 480 mg daily (1 x 240 mg capsule BID)

6.24 In the context of the cost-minimisation approach taken by the submission, DRF may be more costly than some of the alternative treatments (i.e., the 'lower efficacy tier' RRMS DMTs). Since the submission only provided clinical evidence for effectiveness and safety of DRF against DMF, it is not possible to conclude if DRF provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapies.

6.25 The cost minimisation calculation comes from the direct translation of daily equi-effective dose to yearly equi-effective dose, thus the (annual) price parity. No differences in adherence or discontinuation rates for DRF (due to improved GI tolerability of DRF compared to DMF) were assumed. The two drugs have the same administration route (oral) and schedule (twice per day), leading to minimal (if any) difference in drug administration cost.

6.26 Total drug acquisition costs for both DRF and DMF will be directly influenced by the maintenance dose titration (due to adverse events) and temporary discontinuation/dose adherence. The submission implicitly assumed that there is no deviation from the recommended dosage for both drugs but did not fully justify this assumption.

6.27 The submission argued that, in theory, DRF has superior safety that leads to potential cost savings due to reduced health services, as follow:

- The significantly reduced incidence of GI adverse events, which leads to a reduced cost of hospital admissions on a 'per treated patient' basis.
- The significantly reduced treatment discontinuations through cost savings related to fewer neurologist consultations and MRI scans required when ceasing/switching treatments.

6.28 However, these costs were not included in the CMA.

6.29 The relevant PBS-listed alternative treatments for the target population, apart from DMF, include ABCR therapies (including Interferon beta-1a and 1b, and glatiramer acetate), peginterferon beta-1a, and teriflunomide.

6.30 The daily equi-effective maintenance dose for DRF and alternative treatments are:

- DRF 924 mg per day (2 x 231 mg capsules BID) = Teriflunomide 14 mg per day (1 x 14 mg capsule QD). At established equi-effective doses, teriflunomide is currently the least costly alternative at published prices.
- DRF 924 mg per day (2 x 231 mg capsules BID) = Glatiramer acetate 17.14 mg per day (40mg/mL subcutaneous injection, for 3-times-per-week, at least 48 hours apart)
- DRF 924 mg per day (2 x 231 mg capsules BID) = Interferon beta-1a 18.86 mcg per day if subcutaneous injection (44 mcg/mL subcutaneous injection, for 3-times-per-week) OR Interferon beta-1a 4.29 mcg per day (30 mcg/mL intramuscular injection, once per week)
- DRF 924 mg per day (2 x 231 mg capsules BID) = Interferon beta-1b 125 mcg per day (250 mcg subcutaneous injection, every two day)
- DRF 924 mg per day (2 x 231 mg capsules BID) = Peginterferon beta-1a 8.93 mcg per day (125 mcg subcutaneous injection, every two weeks)

6.31 At the time of the submission DMF was the most expensive amongst these PBS-listed drugs. On 1 February 2022, DMF and glatiramer acetate were both subject to statutory price reductions associated with the listing of first generic brands for each of these therapies. Any Special Pricing Arrangements applied to these therapies also ceased at this time. Revised cost minimisation analyses using the evaluation methodology (based on continuing treatment doses only) and the 1 February 2022 prices are presented in the table below for all lower efficacy tier therapies.

Table 8: Cost minimisation of DRF versus 'lower efficacy tier' therapies (based on 1 February 2022 prices)

PBS item	Pack size (days covered)	Daily drug cost	Annual cost	ex-manufacturer price
DRF against Teriflunomide				
DIROXIMEL FUMARATE, 231 mg capsules (continuing)	30	$15.53	$5,670.77	$465.77
PBS item 2898M TERIFLUNOMIDE Tablet 14 mg (continuing)	28	$15.53	$5,670.77	$434.72
DRF against Glatiramer acetate				
DIROXIMEL FUMARATE, 231 mg capsules (continuing)	30	$20.88	$7,627.39	$626.48
PBS item 10416F GLATIRAMER ACETATE SC injection 40 mg/mL single dose pre-filled syringe (continuing)	28	$20.88	$7,627.39	$584.71
DRF against Dimethyl fumarate (DMF)				
DIROXIMEL FUMARATE, 231 mg capsules (continuing)	30	$24.79	$9,096.55	$743.94
PBS item 2966D DIMETHYL FUMARATE, 240 mg capsules (continuing)	28	$24.79	$9,096.55	$694.34
DRF against interferon beta-1a				
DIROXIMEL FUMARATE, 231 mg capsules (continuing)	30	$27.27	$9,959.85	$818.06
PBS item 8968B, 8403G INTERFERON BETA-1A SC injection 44 mcg/0.5 mL single dose pre-filled syringe (continuing)	28	$27.27	$9,959.85	$763.52
PBS item 8805K INTERFERON BETA-1A Intramuscular injection 30 mcg/0.5 mL single dose pre-filled syringe (continuing)	28	$27.27	$9,959.85	$763.52
DRF against interferon beta-1b				
DIROXIMEL FUMARATE, 231 mg capsules (continuing)	30	$29.64	$10,826.86	$889.27
PBS item 8101J INTERFERON BETA-1B SC injection set [15 vials] of 250mcg (continuing)	30	$29.64	$10,826.86	$889.27
DRF against peginterferon beta-1a				
DIROXIMEL FUMARATE, 231 mg capsules (continuing)	30	$31.89	$11,649.00	$956.80
PBS item 10212L, 10220X PEGINTERFERON BETA-1A Single use injection pen 125 mcg/0.5mL (continuing)	28	$31.89	$11,649.00	$893.01

Source: Conducted during the evaluation. Updated by the PBAC Secretariat following 1 February 2022 price publication (accounting for a correction to the DMF price noted in the Pre-PBAC Response).

Abbreviations: AEMP, approved ex-manufacturer price; mg, milligram; mcg, microgram; PBS, Pharmaceutical Benefits Scheme; qty, quantity; SC, subcutaneous

Drug cost/patient/year

6.32 The submission estimated the annual cost of DRF maintenance, based on the proposed published AEMP, as:

- $15,254.41 per patient per year, for 924 mg per day (2 x 231 mg capsules BID).

6.33 Based on 1 February 2022 prices, if DRF is cost-minimised against other alternative treatments for the same target population, the annual cost per patient would range from $5,670.77 (cost minimised against teriflunomide) to $11,649.00 (cost minimised against peginterferon beta-1a).

Estimated PBS usage & financial implications

6.34 This submission was not considered by DUSC.

6.35 The submission applied a market share approach (based on PBS and RPBS prescriptions) to estimate the impact of DRF use on the PBS budget.

6.36 The data sources and key inputs are shown in Table 8 below. The key assumptions of the financial estimates include:

- DRF will only impact the market share of DMF, and that the introduction of DRF will only impact on number of prescriptions of DRF. The submission did not discuss the potential switch from DRF to any of the other drugs for the same target RRMS population. A CMA of DRF against DMF will result in DRF being more expensive than other treatment option for these RRMS patients. If patients switch from other (less expensive) drugs to DRF, this will result in an increased cost to Government.
- Compliance will not be substantially different between DMF and DRF. The assumption of equivalent compliance is uncertain. The submission stated that significantly shorter and less intense GI symptoms with DRF therapy compared to DMF leads to improved adherence.
- Market growth of DMF therapy is based on the observed trend of DMF script volumes 2016 – 2021. While the growth rate has stabilised in the past few years, when DMF was introduced to the market, there was a period of high growth in market share when patients switched from other treatment options to DMF. This might reflect the strong tendency to switch to newer therapies in recent years. Additionally, there has been an overall increasing prevalent population being treated for RRMS (Figure 1, Ocrelizumab RRMS 2020 DUSC Public Release Document[1]). Therefore, while assuming there is no market growth for DRF (based on the stable trend of the DMF scripts in recent years)

[1] https://www.pbs.gov.au/industry/listing/participants/public-release-docs/2020-10/ocrelizumab-relapsing-remitting-MS-analysis-dusc-prd-2020-10v2.PDF

might be reasonable, consideration of a higher growth rate in a sensitivity analysis would have been informative.

6.37 The key driver of utilisation estimates is the (expected) substitution rate of DRF for DMF. Substitution rates were estimated to start at [redacted]% in 2022 and increasing each year to [redacted]% in 2027. The substitution rates from DMF to DRF were based on an internal market analysis by the Sponsor.

Table 9: Key inputs for financial estimates

Data	Value	Source	Comment
PBS dispensed script volumes			
PBS/RPBS DMF market data	Table 4.2.1 in Submission	PBS and RPBS utilisation statistics. Accessed from http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp on 22nd September 2021	This data is reasonable and accurate.
Treatment utilisation			
Substitution (uptake) rates with DRF	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Internal market analysis by Sponsor in consultation with Key Opinion Leaders.	The information could not be verified. The estimate is uncertain.
Market growth of RRMS therapies	Yr 1-6: 0.0%	DUSC 2020 ocrelizumab report; and DMF PSD Nov-19, paragraph.5.3	The report referenced shows that introducing a new drug (ocrelizumab) did not cause the RRMS market to increase from 2018 to 2020. However, the DRF evaluation considers 2022 to 2027. The evaluator cross checked against past market growth. This may be a reasonable assumption for the impacts of the listing of DRF, but as noted in paragraph 6.35 above, the prevalent RRMS treated population is increasing.
Market growth of DMF therapy	Yr 1: 0.0% Yr 2: -2.8% Yr 3: -1.0% Yr 4: -1.0% Yr 5: -2.0% Yr 6: -1.6%	Internal market analysis by Sponsor based on observed trend of DMF script volumes 2016 – 2021.	The information could not be verified. The evaluator cross checked against past market growth. The claim appeared to be reasonable.
Costs			
Drug prices	Table 4.1.3 in Submission	PBS online. Accessed from www.pbs.gov.au on 1st September 2021. Updated alongside Pre-PBAC Response to account for price changes effective 1 February 2022.	Data accessed via https://www.pbs.gov.au/pbs/industry/pricing/ex-manufacturer-price; Max qty (packs) accessed via www.pbs.gov.au. This data is reasonable and accurate.

Data	Value	Source	Comment
Population			
Population growth for Australian adults	Yr 1: 1.6% Yr 2: 1.6% Yr 3: 1.6% Yr 4: 1.6% Yr 5: 1.5% Yr 6: 1.4%	ABS population projections. 3222.0-population projections, Australia, 2017 (base) to 2066 (Series B).	This data is reasonable and accurate.

Source: Table 4.1.1, p128 of the Submission, and compiled during the evaluation.
PBS, Pharmaceutical Benefit Scheme; ABS, Australian Bureau of Statistics; Yr, year; qty, quantity; DMF, dimethyl fumarate; DRF, diroximel fumarate; RRMS, relapsing-remitting multiple sclerosis; DUSC, Drug Utilisation Sub-Committee; PSD, Public Summary Document; RPBS, Repatriation Pharmaceutical Benefits Scheme;.

6.38 DRF has a different pack size to DMF, for both initiating and continuing phases. A substitution rate was calculated to adjust for the difference in pack size, equating to the number of days the pack will last. The initiating script for DMF and DRF both provide two capsules per day for seven days, after which the dose doubles. The initiating pack size for both DMF (28 capsules) and DRF (120 capsules) are greater than the 14 capsules needed for the initiating dose (7 days). The submission did not account for the adjusted dose after the first seven days when calculating the number of days covered by the initiating pack. The error was corrected during the evaluation.

6.39 The Pre-PBAC Response presented updated utilisation and financial estimates, accounting for price changes to DMF and glatiramer acetate which took effect on 1 February 2022, using a placeholder DRF price of $626.48 (the cost minimised price of DRF to glatiramer acetate noted in Table 8 above). These updated estimates were not independently evaluated.

Table 10**: Estimated net cost of DRF to the PBS/RPBS**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total scrips numbers - DRF						
Initial	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Continuing	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total prescriptions	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
PBS/RPBS cost estimates						
PBS/RPBS cost (eff) $	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Less patient copayments $	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Total PBS/RPBS cost (eff) $	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Estimated net cost (eff) of to the PBS/RPBS						
Total net cost to PBS $	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Total net cost to RPBS $	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Total net cost to PBS/RPBS $	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]

DMF, dimethyl fumarate; PBS, Pharmaceutical Benefit Scheme; RBPS, Repatriation Pharmaceutical Benefits Scheme; eff, effective
Prescription numbers and costs using only the corrected initial script substitution rates for 120 mg strength (0.31) are presented. Total prescription numbers differ to those presented in the ESC Advice Table 10 by 1 script for Year 2 – 6 (presumably due to rounding). The difference is negligible on the cost savings.
Source: Attachment 9 Utilisation and cost workbook v4.0 (February 2022)
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 < 5,000*
[3] *5,000 to < 10,000*
[4] *$0 to < $10 million*

6.40 Based on the updated estimates provided in the Pre-PBAC Response, the total cost to the PBS/RPBS of listing DRF was estimated to be $0 to < $10 million in Year 6, and a total of $20 million to < $30 million in the first 6 years of listing. The net save to the PBS using the revised cost minimised price to glatiramer acetate (paragraph 6.40 refers) and the corrected initial prescription substitution rate of 0.31 (compared to 0.23) over the first 6 years of listing was approximately $0 to < $10 million. The estimates assume substitution for DMF only and no impact on the MBS and/or hospital budgets. The proposed savings are driven by the calculated lower price of DRF compared to DMF.

6.41 The submission stated that significantly shorter and less intense GI symptoms with DRF therapy compared to DMF leads to improved adherence. However, the financial estimates assumes that adherence will not be substantially different between DMF and DRF.

6.42 The ESC advised that the methods used to derive the utilisation and financial estimates and the structure of the estimates model were reliable for decision-making and agreed that, if listed on a cost minimisation basis to the least costly relevant alternative, the listing of DRF was likely to be cost neutral or modestly cost saving to the PBS.

Financial Management – Risk Sharing Arrangements

6.43 The submission requested a special pricing arrangement for DRF.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of diroximel fumarate (DRF) for the treatment of relapsing-remitting multiple sclerosis (RRMS). The PBAC considered the claim of non-inferior effectiveness and safety to dimethyl fumarate (DMF) was reasonable. However, the PBAC considered for purposes of satisfying Section 101(3B) of the *National Health Act 1953*, glatiramer acetate, interferon beta-1a (both subcutaneous and intramuscular forms), interferon beta-1b and peg-interferon beta-1a are also relevant alternative therapies. The PBAC's recommendation was therefore, among other matters, based on its assessment that the cost of DRF should be no greater than the cost of DMF or the alternative therapies.

7.2 The PBAC considered it was reasonable to align the restriction wording of DRF with that of DMF, however considered as there is only one dose form and pack size for DRF (including for temporary dose reductions due to adverse events), that it was reasonable to have one listing for DRF, with 5 repeats that would facilitate both initial and continuing treatment. The Committee agreed that, similar to the listing of DMF, an age restriction was not required in the listing of DRF. The PBAC noted a grandfather restriction was requested for DRF and considered this was reasonable and should be reviewed after 12 months post-listing, per standard practice.

7.3 The PBAC considered the nominated primary comparator of DMF, which is chemically similar to DRF, was reasonable. However, the PBAC considered for purposes of satisfying Section 101(3B) of the *National Health Act 1953*, that other relevant alternative therapies include the 'lower efficacy tier' of RRMS therapies, including glatiramer acetate, interferon beta-1a (both subcutaneous and intramuscular forms), interferon beta-1b and peginterferon beta-1a. The Committee noted the arguments in the PSCR that teriflunomide, another lower efficacy tier therapy, is not a relevant alternative therapy on the basis of it being classified as a Pregnancy Category X drug and additional safety concerns, including hepatotoxicity. The PBAC noted pregnancy category may be a relevant consideration in a significant proportion of the MS population given its prevalence in women of childbearing age. The PBAC also noted the safety concerns for teriflunomide, particularly the potential for liver injury and the associated requirement for frequent monitoring of liver function. Overall, the PBAC considered for the purposes of satisfying Section 101(3B) of the *National Health Act 1953* that teriflunomide was not a relevant alternative therapy.

7.4 Based on the evidence presented, which included pharmacokinetic studies, one phase III study (EVOLVE-MS2) and a supportive propensity score-matched indirect analysis of DRF and DMF studies, the PBAC considered the claim of non-inferior comparative effectiveness to DMF was adequately supported. The PBAC also noted that the TGA Delegate was satisfied that DRF and DMF appeared to be bioequivalent in terms of the active metabolite monomethyl fumarate (MMF), through which DRF and DMF exert their effects in RRMS.

7.5 The PBAC considered that, based on the evidence presented, the claim of non-inferior comparative safety to DMF was adequately supported. The Committee noted there was some evidence to suggest some patients may experience a benefit with DRF treatment in terms of gastrointestinal tolerability compared to DMF, and also noted the consumer comments were supportive of the listing of DRF as an alternative to DMF on that basis.

7.6 The PBAC noted the submission presented a cost-minimisation analysis with the equi-effective doses being DRF 924 mg daily and DMF 480 mg daily. The PBAC noted that it was proposed in the pre-PBAC response for the daily cost of DRF to be the same as the daily cost of glatiramer acetate, and that based on current prices, this resulted in a lower price for DRF. The PBAC considered the cost of DRF should be no greater than the cost of DMF or any of the alternative therapies noted in paragraph 7.3 at comparable daily doses as outlined in paragraph 6.30.

7.7 The PBAC considered the listing of DRF for RRMS was likely to be cost neutral or modestly cost saving to the PBS, as it will predominantly replace DMF given the similarity of the two agents, and to a lesser extent, the other noted alternative therapies.

7.8 The PBAC recommended that DRF should be treated as interchangeable on an individual patient basis with DMF, glatiramer acetate, interferon beta-1a (both

subcutaneous and intramuscular forms), interferon beta-1b and peginterferon beta-1a.

7.9 The PBAC advised that DRF is not suitable for prescribing by nurse practitioners, consistent with other PBS listed therapies for RRMS.

7.10 The PBAC recommended that the Early Supply Rule should apply.

7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because DRF is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over DMF or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer	
DIROXIMEL FUMARATE Capsule 231 mg, 120	NEW	1	120	5	Vumerity®	Biogen Australia Pty Ltd

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Level / Method: ☒Authority Required - Streamlined
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Condition: Multiple sclerosis
	Indication: Multiple sclerosis
	Treatment Phase: Initial treatment
	Clinical criteria:

	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised disease modifying therapy for this condition.
	AND
	Clinical criteria:
	Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy for this condition.
	AND
	Clinical criteria:
	Patient must be ambulatory (without assistance or support)
	AND
	Prescribing Instructions: Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.

	Treatment Phase: Continuing treatment
	Clinical criteria:
	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised disease modifying therapy for this condition.
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not show continuing progression of disability while on treatment with this drug
	Prescribing Instructions: Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.

	Treatment Phase: Grandfather treatment
	Clinical criteria:
	Patient must have commenced non-PBS-subsidised treatment with this drug for this PBS indication prior to <<PBS list date>>
	AND
	Clinical criteria:
	The condition must be/have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of at least one of the brain/spinal cord;

	OR The condition must be/have previously been diagnosed as clinically definite relapsing-remitting multiple sclerosis supported by written certification, which is documented in the patient's medical records, from a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient.
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised disease modifying therapy for this condition.
	AND
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
	AND
	Clinical criteria:
	Patient must be ambulatory (without assistance or support)
	Clinical criteria:
	Patient must not show continuing progression of disability while on treatment with this drug
	Prescribing Instructions: Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Biogen welcomes the PBAC decision to recommend VUMERITY (diroximel fumarate) for relapsing-remitting multiple sclerosis. Diroximel fumarate (DRF) adds to the portfolio of multiple sclerosis treatments, to provide further choice to healthcare professionals and those they care for. In making the recommendation, the PBAC considered a different comparator based on its assessment that the cost of DRF should be no greater than the cost of alternative therapies. Biogen will work with the Department of Health to secure a PBS listing for diroximel fumarate as soon as is feasible.