NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Dimethyl Fumarate Te Arai 120 mg modified release capsules
Dimethyl Fumarate Te Arai 240 mg modified release capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dimethyl Fumarate Te Arai 120 mg capsule
Each capsule contains 120 mg Dimethyl Fumarate.

Dimethyl Fumarate Te Arai 240 mg capsule
Each capsule contains 240 mg Dimethyl Fumarate.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dimethyl Fumarate Te Arai 120 mg capsule
Green and white capsules printed with "DMF 120" in black ink on the capsule body.

Dimethyl Fumarate Te Arai 240 mg capsule
Green capsules printed with "DMF 240" in black ink on the capsule body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dimethyl Fumarate is indicated in patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

4.2 Dose and method of administration

Posology
The starting dose for Dimethyl Fumarate is 120 mg twice a day orally. After 7 days, increase to the recommended dose of 240 mg twice a day orally.

Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal (GI) side effects. Within 1 month, the recommended dose of 240 mg twice a day orally should be resumed.

Dimethyl Fumarate can be taken with or without food. For those patients who may experience gastrointestinal or flushing side effects, taking Dimethyl Fumarate with food may improve tolerability. Administration of 325 mg non-enteric coated aspirin prior to Dimethyl Fumarate dosing reduced the occurrence and severity of flushing in a healthy volunteer study (see section 4.5).

Paediatric population
The safety and effectiveness of Dimethyl Fumarate in paediatric patients with multiple sclerosis below the age of 18 have not been established.

Elderly
There are limited data available for the use of Dimethyl Fumarate in patients aged 65 years and over, therefore it is unknown whether elderly patients respond differently to younger patients.

Renal and hepatic impairment
Dimethyl Fumarate has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology studies, no dose adjustments are needed.

Method of administration
The capsule or its contents should not be crushed, divided or dissolved as the enteric coating of the microtablets prevents irritant effects on the gut.

4.3 Contraindications

Dimethyl Fumarate is contraindicated in patients with known hypersensitivity to DMF or any excipients listed in section 6.1. Suspected or confirmed Progressive Multifocal Leukoencephalopathy (PML).

4.4 Special warnings and precautions for use

Infection
Decreases in lymphocyte counts observed in patients treated with Dimethyl Fumarate in clinical trials were not associated with increased frequencies of infections. However, due to the risk of serious, possibly fatal infection, patients who develop lymphopenia as a result of treatment with Dimethyl Fumarate require close monitoring. Patients should be instructed to report symptoms of infection to their physician. For patients with signs and symptoms of serious infections, interrupting treatment with Dimethyl Fumarate should be considered until the infection(s) resolves.

Lymphopenia
Dimethyl Fumarate may decrease lymphocyte counts (see section 4.8). In the MS placebo controlled trials, mean lymphocyte counts decreased by approximately 30% during the first year of treatment with Dimethyl Fumarate and then remained stable. WBC counts <3.0 x 10^9/L and lymphocyte counts <0.5 x 10^9/L were reported in 6 to 7% of subjects given Dimethyl Fumarate. Prior to initiating treatment with Dimethyl Fumarate, a recent complete blood count (CBC) including lymphocytes (i.e. within 3 months) is to be completed. A CBC, including lymphocytes, is recommended, after 3 months of treatment and every 3 months thereafter, and as clinically indicated.

Enhanced vigilance due to an increased risk for Progressive Multifocal Leukoencephalopathy (PML) is recommended in patients with lymphopenia as follows:

- Dimethyl Fumarate should not be initiated in patients with severe lymphopenia (lymphocyte counts < 0.5 x 10^9/L).
- Dimethyl Fumarate should be discontinued in patients with severe lymphopenia (lymphocyte counts < 0.5 x 10^9/L).
- In patients with moderate reductions of absolute lymphocyte counts ≥ 0.5 x 10^9/L to < 0.8 x 10^9/L, the benefit/risk of Dimethyl Fumarate treatment should be re-assessed.
- In patients with lymphocyte counts below lower limit of normal (LLN) as defined by local laboratory reference range, regular monitoring of absolute lymphocyte counts is recommended. Additional factors that might further augment the individual PML risk should

be considered (see subsection on PML below).

Lymphocytes counts should be followed until recovery

Progressive Multifocal Leukoencephalopathy (PML)
PML has been reported in patients treated with Dimethyl Fumarate. PML is an opportunistic infection caused by John-Cunningham virus (JCV), which may be fatal or result in severe disability.
PML cases have occurred with dimethyl fumarate and other medicinal products containing fumarates in the setting of lymphopenia (lymphocyte counts below LLN). Moderate to severe lymphopenia appears to increase the risk of PML with Dimethyl Fumarate, however, risk cannot be excluded in patients with mild lymphopenia.

Additional factors that might contribute to an increased risk for PML in the setting of lymphopenia are:

- duration of Dimethyl Fumarate therapy. Cases of PML have occurred after approximately 1 to 5 years of treatment, although the exact relationship with duration of treatment is unknown.
- profound decreases in CD4+ and especially in CD8+ T cell counts, which are important for immunological defense, and
- prior immunosuppressive or immunomodulatory therapy (see below).

Physicians should evaluate their patients to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are typical of MS or possibly suggestive of PML.

At the first sign or symptom suggestive of PML, Dimethyl Fumarate should be withheld and appropriate diagnostic evaluations, including determination of JCV DNA in cerebrospinal fluid (CSF) by quantitative polymerase chain reaction (PCR) methodology, need to be performed. The symptoms of PML may be similar to an MS relapse. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. Physicians should be particularly alert to symptoms suggestive of PML that the patient may not notice. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

PML can only occur in the presence of a JCV infection. It should be considered that the influence of lymphopenia on the accuracy of serum anti-JCV antibody testing has not been studied in dimethyl fumarate treated patients. It should also be noted that a negative anti-JCV antibody test (in the presence of normal lymphocyte counts) does not preclude the possibility of subsequent JCV infection.

If a patient develops PML, Dimethyl Fumarate must be permanently discontinued.

Anaphylactic reactions
Cases of anaphylaxis have been reported following Dimethyl Fumarate administration. These reactions generally occurred after the first dose, but may occur at any time during treatment, and may be serious and life threatening. Patients should be instructed to discontinue Dimethyl Fumarate and seek immediate medical care if they experience signs or symptoms of anaphylaxis. Treatment should not be restarted (see section 4.8).

Herpes Zoster Infections
Serious cases of herpes zoster have occurred with Dimethyl Fumarate, including disseminated herpes

zoster, herpes zoster ophthalmicus, herpes zoster meningoencephalitis and herpes zoster meningomyelitis. These events may occur at any time during treatment. Monitor patients on Dimethyl Fumarate for signs and symptoms of herpes zoster. If herpes zoster occurs, appropriate treatment for herpes zoster should be administered. Consider withholding Dimethyl Fumarate treatment in patients with serious infections until the infection has resolved (see Section 4.8).

Vaccination

Patients taking Dimethyl Fumarate may receive non-live vaccines (see Section 4.5). The safety of administration of live attenuated vaccines during treatment with Dimethyl Fumarate has not been evaluated in clinical trials. Live vaccines have a potential risk of clinical infection and are not recommended during treatment with Dimethyl Fumarate.

Renal function

In clinical trials with patients with multiple sclerosis, adverse events of proteinuria (proteinuria, microalbuminuria and urine albumin present) were reported at slightly higher frequencies in patients treated with Dimethyl Fumarate compared to patients that received placebo. The significance of these clinical observations is not known at this time.

Prior to initiating treatment with Dimethyl Fumarate, urinalysis should be available (within 6 months prior to starting therapy). During treatment, urinalysis is recommended annually and as clinically indicated.

The use of Dimethyl Fumarate in patients who receive chronic treatment with medications that are associated with potential nephrotoxic risk (e.g., aminoglycosides, diuretics, NSAIDs, lithium) has not been evaluated. Therefore, caution should be exercised if Dimethyl Fumarate is used in patients receiving chronic treatment with such medications.

Haematological

In the placebo-controlled studies, most patients (>98%) had normal lymphocyte values prior to initiating treatment. Upon treatment with Dimethyl Fumarate, lymphocytes counts decreased over the first year with a subsequent plateau. On average, lymphocyte counts decreased by approximately 30% of baseline value. Mean and median lymphocyte counts remained within normal limits. Patients with lymphocyte counts $<0.5x10^9/L$ were observed in <1% of patients treated with placebo and 6% of patients treated with Dimethyl Fumarate. In controlled and uncontrolled clinical studies, 2% of patients experienced lymphocyte counts $<0.5 \times 10^9/L$ for at least six months. In these patients, the majority of lymphocyte counts remained $<0.5 \times 10^9/L$ with continued therapy.

The incidence of infections (58% vs 60%) and serious infections (2% vs 2%) was similar in patients treated with placebo or Dimethyl Fumarate, respectively. An increased incidence of infections and serious infections was not observed in patients with lymphocyte counts
$<0.8x10^9/L$ or $0.5x10^9/L$. A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.

Effect on Laboratory Tests

There are no data available on whether Dimethyl Fumarate interferes with laboratory tests.

4.5 Interaction with other medicines and other forms of interaction

During treatment with Dimethyl Fumarate, simultaneous use of other fumaric acid derivatives (topical or systemic) should be avoided as such clinical scenarios have not been studied.

In humans, Dimethyl Fumarate is extensively metabolised by esterases before it reaches the systemic circulation and further metabolism occurs through the tricarboxylic acid (TCA) cycle, with no involvement of the cytochrome P450 (CYP) system. Potential drug interaction risks were not identified from *in vitro* CYP-inhibition and induction studies, a p-glycoprotein study, or studies of the protein binding of DMF and MMF.

A pharmacokinetic study with a combined oral contraceptive has been performed with Dimethyl Fumarate (Dimethyl Fumarate). There were no relevant effects of Dimethyl Fumarate on the pharmacokinetic profile of norelgestromin and ethinyl estradiol. No interaction studies have been performed with oral contraceptives containing other progestogens; however, an effect of Dimethyl Fumarate on their exposure is not expected.

Commonly used drugs in patients with multiple sclerosis, intramuscular (IM) interferon beta- 1a and GA, were clinically tested for potential drug-interactions with Dimethyl Fumarate and did not alter the pharmacokinetic profile of Dimethyl Fumarate. Aspirin (non-enteric coated), 325 mg, when administered approximately 30 minutes before Dimethyl Fumarate, did not alter the pharmacokinetic profile of Dimethyl Fumarate.

Patients treated with Dimethyl Fumarate were able to mount an effective immune response to inactivated neoantigen (first vaccination), recall antigen (re-exposure), or polysaccharide antigen in a clinical study in patients with relapsing forms of MS. This response was comparable to patients treated with non-pegylated interferons. Patients taking Dimethyl Fumarate may receive non-live vaccines. No clinical data are available on the efficacy and safety of live attenuated vaccines in patients taking Dimethyl Fumarate.

4.6 Fertility, pregnancy and lactation

Pregnancy
Australian categorisation system for prescribing medicines in pregnancy: Category B1

The effects of Dimethyl Fumarate on labour and delivery are unknown. In rats given oral Dimethyl Fumarate from early gestation to the end of lactation, there were no effects on delivery at doses up to 250 mg/kg/day (9 times the MRHD based on AUC).

Dimethyl Fumarate should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus.

Breast-feeding
It is not known whether this drug is excreted in milk. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Dimethyl Fumarate treatment. The benefit of breast-feeding for the child and the benefit of treatment for the woman should be taken into account.

Fertility
Data from nonclinical studies do not suggest that Dimethyl Fumarate would be associated with an increased risk of reduced fertility.

Administration of DMF to male rats at daily oral doses of up to 7-9 times the maximum recommended human dose (MRHD) based on mg/m^2 prior to and during mating had no effects on fertility. Administration of DMF to female rats at daily oral doses of up to 5-6 times the MRHD based on mg/m^2

prior to and during mating, and continuing to Day 7 of gestation, delayed oestrus cycling at the highest dose but had no effects on fertility.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been conducted.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions (incidence ≥10% and >2% than placebo) for Dimethyl Fumarate were flushing and gastrointestinal (GI) events (i.e. diarrhoea, nausea, abdominal pain, upper abdominal pain).

The most commonly reported adverse events leading to discontinuation (incidence >1%) in patients treated with Dimethyl Fumarate were flushing (3%) and gastrointestinal events (4%).

In placebo-controlled and uncontrolled clinical studies, a total of 2468 patients have received Dimethyl Fumarate and been followed for periods up to 4 years with an overall exposure equivalent to 3588 person-years. Approximately 1056 patients have received more than 2 years of treatment with Dimethyl Fumarate. The experience in uncontrolled clinical trials is consistent with the experience in the placebo-controlled clinical trials.

Tabulated summary of adverse reactions
In the two Phase 3 placebo-controlled trials, 1529 patients received Dimethyl Fumarate with an overall exposure of 2371 person-years (see section 5.1). The adverse reactions presented in the table below are based on safety information from 769 patients treated with Dimethyl Fumarate 240 mg twice a day and 771 patients treated with placebo.

The adverse reactions are presented as MedDRA preferred terms under the MedDRA system organ class.

The incidence of the adverse reactions below is expressed according to the following categories:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)

Table 1: Adverse Reactions in Study 1 and 2 reported for Dimethyl Fumarate

MedDRA System Organ Class	**Frequency**	
	Very Common (≥1/10)	**Common (≥1/100 to <1/10)**
Infections and Infestations		Gastroenteritis
Blood and Lymphatic System Disorders		Lymphopenia Leucopenia
Nervous System Disorders		Burning sensation
Vascular Disorders	Flushing	Hot Flush

Gastrointestinal Disorders	Diarrhoea Nausea Abdominal Pain Upper Abdominal Pain	Vomiting Dyspepsia Gastritis Gastrointestinal disorder
Skin and Subcutaneous Tissue Disorders		Pruritus Rash Erythema
Renal and Urinary Disorders		Proteinuria
General Disorders and Administration Site Conditions		Feeling hot
Investigations		Albumin urine present Aspartate aminotransferase increased Alanine aminotransferase increased White blood cell count decreased

Table 2: Adverse Reactions in Study 1 and 2 reported for Dimethyl Fumarate 240 mg BID at ≥ 2% higher incidence than placebo

Primary System Organ Class Preferred Term	**Dimethyl Fumarate 240 mg BID n=769 %**	**Placebo n=771 %**
Blood and Lymphatic System Disorders		
Lymphopenia	2	<1
Gastrointestinal Disorders		
Diarrhoea	14	11
Nausea	12	9
Abdominal pain upper	10	6
Abdominal pain	10	5
Vomiting	9	5
Dyspepsia	5	3
Vascular Disorders		
Flushing	35	4
Hot Flush	7	2
Skin and Subcutaneous Tissue Disorders		
Pruritus Rash Erythema	8 8 5	4 3 1
Investigations		
Albumin urine present	6	4
Aspartate aminotransferase increased	4	2

Other relevant ADRs (<2% difference) include: gastroenteritis, gastritis, gastrointestinal disorder, burning sensation, feeling hot, alanine aminotransferase increased, proteinuria, white blood cell count decreased and leucopenia.

Description of selected adverse reactions

Flushing

The incidence of patients with flushing events (e.g. warmth, redness, itching, burning sensation) was higher early in the course of treatment (primarily in month 1) and decreased over time, which might indicate that this symptom became less prevalent with continued use. In patients with flushing, the majority had flushing events that were mild or moderate in severity. Overall, 3% of patients treated with Dimethyl Fumarate discontinued due to flushing. The incidence of serious flushing which may be characterised by generalised erythema, rash and/or pruritus was seen in less than 1% of patients treated with Dimethyl Fumarate (see section 4.2).

Gastrointestinal

The incidence of patients with GI events (e.g. nausea, vomiting, diarrhoea, abdominal pain, upper abdominal pain & dyspepsia) was higher early in the course of treatment (primarily in month 1) and decreased over time in patients treated with Dimethyl Fumarate compared with placebo. Four percent (4%) of patients treated with Dimethyl Fumarate discontinued due to gastrointestinal events. The incidence of serious GI events, including gastroenteritis and gastritis, was seen in less than 1% of patients treated with Dimethyl Fumarate.

Hepatic transaminases

In placebo-controlled studies, elevations of hepatic transaminases were observed. The majority of patients with elevations had hepatic transaminases that were < 3 times the upper limit of normal (ULN). The increased incidence of elevations of hepatic transaminases in patients treated with Dimethyl Fumarate relative to placebo was primarily seen during the first 6 months of treatment. Elevations of alanine aminotransferase and aspartate aminotransferase ≥ 3 times ULN, respectively, were seen in 5% and 2% of patients treated with placebo and 6% and 2% of patients treated with Dimethyl Fumarate. Discontinuations due to elevated hepatic transaminases were <1% and similar in patients treated with Dimethyl Fumarate or placebo. Elevations in transaminases ≥ 3 times ULN with concomitant elevations in total bilirubin > 2 times ULN were not observed during placebo-controlled studies but have been observed in the post-marketing experience (see section 4.8).

Post marketing experience

In post marketing experience, hypersensitivity reactions including urticaria, angioedema, and difficulty breathing have been reported following Dimethyl Fumarate administration. Cases of anaphylaxis have also been reported (see section 4.4).

Progressive multifocal leukoencephalopathy has occurred in the setting of lymphopenia (<0.91 x 10^9/L) following Dimethyl Fumarate administration. These PML cases have occurred predominantly in the setting of prolonged moderate to severe lymphopenia (see Section 4.4).

Liver function abnormalities (elevations in transaminases ≥ 3 times ULN with concomitant elevations in total bilirubin > 2 times ULN) have been reported following Dimethyl Fumarate administration in post marketing experience. These abnormalities resolved upon treatment discontinuation over a varying period of time. Therefore, ongoing monitoring of LFTs is recommended in patients being treated with Dimethyl Fumarate, as clinically indicated.

Herpes zoster infection has been reported with Dimethyl Fumarate administration in post marketing experience. The majority of cases were non-serious (see Section 4.4).

Rhinorrhoea and alopecia have been reported with Dimethyl Fumarate administration in post marketing experience.

Reporting of suspected adverse events

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Cases of overdose with Dimethyl Fumarate have been reported. There are no known therapeutic interventions to enhance elimination of Dimethyl Fumarate nor is there a known antidote. In the event of overdose, it is recommended that symptomatic supportive treatment be initiated as clinically indicated.

Contact the National Poisons Centre on 0800 POISON (0800 764 766) for advice on management of overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
The mechanism by which DMF exerts therapeutic effects in multiple sclerosis is not fully understood. Nonclinical studies indicate that pharmacodynamic responses to DMF appear to be mediated, at least in part, through activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway, which is a critical cellular defence system for responding to a variety of potentially toxic stimuli through up-regulation of antioxidant response genes.

Pharmacodynamic effects
Activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway
Biological response markers of Nrf2 activation (e.g. NAD(P)H dehydrogenase, quinone 1 [NQO1]) are detected at elevated levels in blood from patients with multiple sclerosis following 12 or 48 weeks of oral dosing with DMF. These clinical data appear to be consistent with nonclinical studies demonstrating DMF-dependent up-regulation of Nrf2 antioxidant response genes in multiple tissue types, although the magnitude of up-regulation observed in tissues of the central nervous system was small. The relationships between blood NQO1 levels and the mechanism(s) by which DMF exerts its effects in multiple sclerosis are unknown.

Effects on the immune system
In nonclinical and clinical studies, DMF demonstrates anti-inflammatory and immunomodulatory properties. DMF and monomethyl fumarate (MMF), the primary metabolite of DMF, significantly reduce immune cell activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli, and moreover affects lymphocyte phenotypes through a down-regulation of pro-inflammatory cytokine profiles (T_H1, T_H17), and biases towards anti-inflammatory production (T_H2). DMF demonstrates therapeutic activity in models of inflammatory and neuroinflammatory injury, and also appears to promote improvement in blood brain barrier integrity. All of these anti-inflammatory effects appear consistent with the significant clinical activity of DMF in reducing brain lesions and relapses in multiple sclerosis patients.

Effects on Central Nervous System
In nonclinical studies MMF was shown to penetrate into the central nervous system where it promotes cyto- and neuro-protective responses. DMF and/or MMF significantly improve cell viability after oxidative challenge in primary cultures of astrocytes and neurons, suggesting that DMF and MMF prevent neurodegeneration in response to toxic stress. DMF showed therapeutic benefit in acute neurotoxic injury models and models of neurodegenerative disease. These nonclinical data combined with imaging and functional endpoints from clinical studies suggest DMF may promote a

neuroprotective benefit in the central nervous system.

Effect on cardiovascular system

Single doses of 240 mg or 360 mg DMF did not have any effect on the QTc interval when compared to placebo in a thorough QTc study.

Clinical efficacy and safety

The efficacy and safety of Dimethyl Fumarate was demonstrated in two studies that evaluated Dimethyl Fumarate taken either twice or three times a day in patients with relapsing-remitting multiple sclerosis (RRMS).

The starting dose for Dimethyl Fumarate was 120 mg twice or three times a day for the first 7 days, followed by an increase to either 240 mg twice or three times a day. Both studies included patients with Expanded Disability Status Scale (EDSS) scores ranging from 0 to 5, who had experienced at least 1 relapse during the year prior to randomisation, or, within 6 weeks of randomisation had a brain Magnetic Resonance Imaging (MRI) demonstrating at least one gadolinium-enhancing (Gd+) lesion.

Study 1 (DEFINE) was a 2-year randomised, double-blind, placebo-controlled study in 1234 patients with RRMS who had not received interferon-beta or glatiramer acetate (GA) for at least the previous 3 months or natalizumab for at least the previous 6 months. Neurological evaluations were performed at baseline, every 3 months and at time of suspected relapse. MRI evaluations were performed at baseline, month 6, and year 1 and 2. The primary endpoint in Study 1 was the reduction in the proportion of patients relapsed at 2 years. Patients were randomised to receive Dimethyl Fumarate 240 mg twice a day (n=410), Dimethyl Fumarate 240 mg three times a day (n=416), or placebo (n=408) for up to 2 years. Median age: 39 years, median years since diagnosis: 4.0 years and median EDSS score at baseline: 2.0. Median time on study was 96 weeks for all three treatment groups.

The proportion of patients relapsed was significantly lower in the group treated with Dimethyl Fumarate than in the group treated with placebo at 2 years. Secondary endpoints at 2 years included the number of new or newly enlarging T2 hyperintense lesions, number of Gd-enhancing lesions, annualised relapse rate (ARR), and time to confirmed disability progression. Confirmed disability progression was defined as at least a 1 point increase from baseline EDSS (1.5 point increase for patients with baseline EDSS of 0) sustained for 12 weeks. Dimethyl Fumarate had a clinically meaningful and statistically significant effect on all primary and secondary study endpoints. The 240 mg three times daily dose resulted in no additional benefit over the Dimethyl Fumarate 240 mg twice daily dose.

The results for this study are shown in Table 3.

Table 3: Clinical and MRI Results of Study 1

	Dimethyl Fumarate 240 mg BID (n=410)	**Placebo (n=408)**	**P-value**
Clinical Endpoints			
Annualised relapse rate Relative reduction (percentage) (95% CI)	0.172 53% (39%, 64%)	0.364	<0.0001
Proportion relapsing(a)	0.270	0.461	<0.0001
Hazard ratio for first relapse	0.51		

(95% CI)	(0.40, 0.66)		
Proportion with disability progression(a)	0.164	0.271	0.0050
Hazard ratio for progression (95% CI)	0.62 (0.44, 0.87)		
MRI Endpoint	n=152	n=165	
Number of new or newly enlarging T2 lesions over 2 years Mean (median)	3.2 (1.0)	16.5 (7.0)	<0.0001
Relative reduction (percentage) (95% CI)	85% (77%, 90%)		
Percentage of subjects with			
0 lesions 1 lesion 2 lesions 3 lesions 4 or more lesions	45% 17% 9% 7% 22%	27% 5% 2% 5% 61%	
Number of Gd lesions at 2 years Mean (median)	0.1 (0)	1.8 (0)	
Percentage of subjects with			
0 lesions 1 lesion 2 lesions 3 to 4 lesions 5 or more lesions	93% 5% <1% 0 <1%	62% 10% 8% 9% 11%	
Relative odds reduction			
(percentage) (95% CI	90% (78%, 95%)		<0.0001
Number of new T1 hypointense lesions over 2 years Mean (median)	2.0 (1.0)	5.7 (2.0)	< 0.0001
Relative reduction (percentage) (95% CI)	72% (61%, 80%)		
Percentage of subjects with 0 lesions 1 lesion 2 lesions 3 to 4 lesions 5 or more lesions	40% 23% 10% 17% 9%	36% 10% 6% 12% 37%	

(a): Based on Kaplan-Meier estimate.
Note: All analyses of clinical endpoints were intent-to-treat. MRI analysis used MRI cohort.

Study 2 (CONFIRM) was a 2-year multicenter, randomised, double-blind, placebo-controlled study which contained a rater-blinded (i.e. study physician/investigator assessing the response to study treatment is blinded) reference comparator of glatiramer acetate (GA) in 1417 patients with RRMS.

Patients had not received interferon-beta for at least the previous 3 months, natalizumab for at least the previous 6 months and had not previously received GA. The efficacy and safety evaluations were similar to Study 1 and the endpoints were broadly consistent, but the primary endpoint of Study 2 was the annualized relapse rate at 2 years, whereas the primary endpoint of Study 1 was the proportion of subjects relapsed at 2 years. Median age: 37 years, median years since diagnosis: 3.0 years and median EDSS score at baseline: 2.5. Patients were randomised to receive Dimethyl Fumarate 240 mg twice a day (n=359), Dimethyl Fumarate 240 mg three times a day (n=344), placebo (n=363) or glatiramer acetate (n=351) for up to 2 years. Median time on study was 96 weeks for all treatmentgroups.

The annualised relapse rate was significantly lower in patients treated with Dimethyl Fumarate than in patients treated with placebo at 2 years. Secondary endpoints at 2 years included the number of new or newly enlarging T2 hyperintense lesions, number of T1 hypointense lesions, proportion of patients relapsed and time to confirm disability progression defined as in Study 1.

Dimethyl Fumarate had a clinically meaningful and statistically significant effect on the primary endpoint and secondary relapse and MRI endpoints. In Study 2, the annualised relapse rate for glatiramer acetate versus placebo was 0.286 and 0.401, corresponding to a reduction of 29% (p=0.013) which is consistent with approved product labelling. The results for thisstudy are shown in Table 4.

Table 4: Clinical and MRI Results of Study 2

	Dimethyl Fumarate 240 mg BID (n=359)	**Placebo (n=363)**	**GA (n=350)**
Clinical Endpoints			
Annualised relapse rate	0.224	0.401	0.286
Relative reduction (percentage)	44%		29%
(95% CI)	(26%, 58%)		(7%, 45%)
P-value versus placebo	<0.0001		0.0128
Proportion relapsing (a)	0.291	0.410	0.321
Hazard ratio for first relapse	0.66		0.71
(95% CI)	(0.51, 0.86)		(0.55, 0.92)
P-value versus placebo	0.0020		0.0097
Proportion with disability progression (a)	0.128	0.169	0.156
Hazard ratio	0.79		0.93
(95% CI)	(0.52, 1.19)		(0.63, 1.37)
P-value versus placebo	0.2536		0.7036
MRI Endpoint	**n=147**	**n=144**	**n=161**
Number of new or newly enlarging T2 lesions over 2 years			
Mean (median)	5.7 (2.0)	19.9 (11.0)	9.6 (3.0)
Relative reduction (percentage)	71%		54%
(95% CI)	(59%, 79%)		(37%, 67%)
P-value versus placebo	<0.0001		<0.0001
Percentage of subjects with			
0 lesions	27%	12%	24%

1 lesion 2 lesions 3 lesions 4 or more lesions	17% 11% 8% 36%	5% 3% 4% 76%	14% 8% 6% 48%
Number of Gd lesions at 2 years			
Mean (median)	0.5 (0.0)	2.0 (0.0)	0.7 (0.0)
Percentage of subjects with			
0 lesions	80%	61%	77%
1 lesion	11%	17%	12%
2 lesions	3%	6%	4%
3 to 4 lesions	3%	2%	2%
5 or more lesions	3%	14%	6%
Relative odds reduction			
(percentage)	74%		61%
(95% CI)	(54%, 85%)		(35%, 76%)
P-value versus placebo	<0.0001		0.0003
Number of new T1 hypointense lesions over 2 years			
Mean (median)	3.8 (1.0)	8.1 (4.0)	4.5 (2.0)
Relative reduction (percentage)	57%		41%
(95% CI)	(39%, 70%)		(18%, 58%)
P-value versus placebo	<0.0001		0.0021
Percentage of subjects with			
0 lesions	39%	21%	34%
1 lesion	15%	6%	12%
2 lesions	11%	7%	14%
3 to 4 lesions	9%	21%	12%
5 or more lesions	26%	45%	27%

(a): Based on Kaplan-Meier estimate.
Note: All analyses of clinical endpoints were intent-to-treat. MRI analysis used MRI cohort.

Pooled results at 2 years for Study 1 and Study 2 showed consistent and statistically significant results for Dimethyl Fumarate versus placebo in all primary and secondary endpoints, including time to confirmed disability progression (32% relative reduction compared to placebo).

5.2 Pharmacokinetic properties

Orally administered Dimethyl Fumarate undergoes rapid presystemic hydrolysis by esterases and is converted to its primary metabolite, MMF, which is also active. DMF is not quantifiable in plasma following oral administration of Dimethyl Fumarate. Therefore, all pharmacokinetic analyses related to Dimethyl Fumarate were performed with plasma MMF concentrations. Pharmacokinetic data were obtained in subjects with multiple sclerosis and healthy volunteers.

Absorption
The T_{max} of Dimethyl Fumarate is 2-2.5 hours. As Dimethyl Fumarate microtablets are protected by

an enteric coating, absorption does not commence until the microtablets leave the stomach (generally less than 1 hour). Following 240 mg administered twice a day with food, the median peak (C_{max}) was 1.72 mg/L and overall (AUC) exposure was 8.02 h.mg/L in subjects with MS. C_{max} and AUC increased approximately dose proportionally in the dose range studied (120 mg to 360 mg).

Food does not have a clinically significant effect on exposure of Dimethyl Fumarate. Therefore, Dimethyl Fumarate may be taken with or without food.

Distribution
The apparent volume of distribution following oral administration of 240 mg Dimethyl Fumarate varies between 60 and 90 L. Human plasma protein binding of MMF generally ranges between 27%-40%.

Biotransformation
In humans, Dimethyl Fumarate is extensively metabolised by esterases, which are ubiquitous in the gastrointestinal tract, blood and tissues, before it reaches the systemic circulation. Further metabolism occurs through the tricarboxylic acid (TCA) cycle, with no involvement of the cytochrome P450 (CYP) system. A single 240 mg ^{14}C-DMF dose study identified monomethyl fumarate, fumaric and citric acid, and glucose as the major metabolites in plasma. The downstream metabolism of fumaric and citric acid occurs through the TCA cycle, with exhalation of CO_2 serving as a primary route of elimination.

Elimination
Exhalation of CO_2 is the primary route of Dimethyl Fumarate elimination accounting for approximately 60% of the dose. Renal and faecal elimination are secondary routes of elimination, accounting for 15.5% and 0.9% of the dose respectively.

The terminal half-life of MMF is short (approximately 1 hour) and no circulating MMF is present at 24 hours in the majority of individuals. Accumulation of parent drug or MMF does not occur with multiple doses of Dimethyl Fumarate at the therapeutic regimen.

Linearity
Dimethyl Fumarate exposure increases in an approximately dose proportional manner with single and multiple doses in the 120 to 360 mg dose range studied.

Pharmacokinetics in special patient groups
Based on the results of ANOVA, body weight is the main covariate of exposure (by C_{max} and AUC) in relapsing remitting multiple sclerosis (RRMS) subjects, but did not affect safety and efficacy measures evaluated in the clinical studies. Gender and age did not have a statistically significant impact on C_{max} and AUC.

Race
Race and ethnicity have no effect on the pharmacokinetics of Dimethyl Fumarate.

Renal Impairment
Since the renal pathway is a secondary route of elimination for Dimethyl Fumarate, accounting for less than 16% of the dose administered, evaluation of pharmacokinetics in individuals with renal impairment was not conducted.

Hepatic Impairment
As DMF and MMF are metabolised by esterases, without the involvement of the CYP450 system, evaluation of pharmacokinetics in individuals with hepatic impairment was not conducted.

5.3 Preclinical safety data

Genotoxicity
DMF and MMF were negative in the following *in vitro* assays (bacterial reverse mutation test, chromosomal aberration assay in human lymphocytes, and [DMF only] a forward mutation assay in Chinese hamster ovary cells) and *in vivo* assays (rat micronucleus assay with DMF, bone marrow cytogenetic test with MMF). Results did not suggest a risk of genotoxicity in patients.

Carcinogenicity
Carcinogenicity studies were conducted in mice and rats with oral dosing with DMF for up to 2 years. Doses in mice were 25, 75, 200 and 400 mg/kg/day and in rats were 25, 50, 100 and 150 mg/kg/day.

Incidences of tumours in the nonglandular stomach were increased in mice and rats (squamous cell papillomas and carcinomas in mice and rats; leiomyosarcomas and fibrosarcomas in mice). As the nonglandular stomach of mice and rats does not have a human counterpart, these tumours are not considered to be a risk in patients.

Incidences of renal tubular adenomas (benign) and carcinomas were increased in both mice and rats. Higher incidences of at least one of these tumours were observed at doses of 75 mg/kg/day in mice (1.3 times the MRHD based on AUC) and 100 mg/kg/day in rats (2 times the MRHD based on AUC), with significantly higher incidences at 200 mg/kg/day in mice and 150 mg/kg/day in rats (4 times the MRHD in both species). The clinical relevance of these findings is unclear but they might pose a human risk.

In male rats, an increase in the incidence of benign interstitial cell (Leydig cell) adenoma of the testes was observed at ≥100 mg/kg/day (2 times the MRHD based on AUC). The rat is particularly sensitive to developing this tumour type and the relevance of these findings to human risk is considered low.

Reproduction toxicity
Oral treatment of pregnant rats and rabbits during the period of organogenesis with Dimethyl Fumarate showed no evidence of teratogenicity. In rats, the high dose of 250 mg/kg/day (9 times the MRHD based on AUC) reduced foetal weight and caused minor impairment of ossification in foetuses, concomitant with maternal toxicity; the no-effect dose for foetal effects was 100 mg/kg/day (4 times the MRHD based on AUC). In rabbits, the high dose of 150 mg/kg/day (14 times the MRHD based on AUC) elicited toxicity and abortions in does, but did not affect embryofoetal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Povidone
Crospovidone
Colloidal anhydrous silica
Magnesium stearate
SheffCoat Clear ASA 5X00294 (Hydroxypropyl methyl cellulose, Triacetin, Talc)

SheffCoat White ENT TEC 5X00273 (Methacrylic acid/ethylacrylate 1:1 copolymer, Talc, Titanium dioxide, Triethyl citrate)
Gelatin
Titanium dioxide
Brilliant blue FCF-FD&C
Iron oxide yellow
Iron oxide black
Shellac
Propylene glycol
Strong ammonia solution
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

120 mg modified release capsules: 36 months
240 mg modified release capsules: 36 months

6.4 Special precautions for storage

Store below 30°C.
Store in original packaging in order to protect from light.

6.5 Nature and contents of container

120 mg capsules: 14 or 56 capsules in aluminium blister strips.
240 mg capsules: 14 or 56 capsules in aluminium blister strips. .

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Te Arai BioFarma Limited
PO Box 46205, Herne Bay
Auckland, 0975

0800 TEARAI (832 724)

9. DATE OF FIRST APPROVAL

13 January 2023

9. DATE OF REVISION OF THE TEXT

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
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