AUSTRALIAN PRODUCT INFORMATION

TECFIDERA® (dimethyl fumarate) modified release capsules

1 NAME OF THE MEDICINE

Dimethyl fumarate (DMF).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TECFIDERA (dimethyl fumarate [DMF]) is formulated as enteric coated microtablets enclosed within hard gelatin capsules, containing the active ingredient dimethyl fumarate.

Each TECFIDERA capsule contains 120 mg or 240 mg DMF. The inactive ingredients of TECFIDERA are: microcrystalline cellulose, croscarmellose sodium, purified talc, colloidal anhydrous silica, magnesium stearate, triethyl citrate, methylacrylate-methyl methacrylate copolymer, methacrylic acid – ethyl acrylate copolymer (1:1), simethicone, sodium lauryl sulfate, polysorbate 80, gelatin, titanium dioxide, brilliant blue FCF (CI42090), iron oxide yellow (CI77492), iron oxide black (CI77499).

3 PHARMACEUTICAL FORM

Modified release capsules.

120 mg capsules:
TECFIDERA is supplied as green and white capsules printed with “BG-12 120 mg” in black ink on the capsule body. Each capsule contains 120 mg DMF.

240 mg capsules:
TECFIDERA is supplied as green capsules printed with “BG-12 240 mg” in black ink on the capsule body. Each capsule contains 240 mg DMF.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TECFIDERA 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

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

The capsule or its contents should not be crushed, divided, or dissolved as the enteric coating of the micro-tablets prevents irritant effects on the gut.

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.

TECFIDERA can be taken with or without food. For those patients who may experience gastrointestinal or flushing side effects, taking TECFIDERA with food may improve tolerability.

Administration of 325 mg non-enteric coated aspirin prior to TECFIDERA dosing reduced the occurrence and severity of flushing in a healthy volunteer study (see Section 4.5 Interactions with other medicines and other forms of interactions).

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

4.3 CONTRAINDICATIONS

TECFIDERA is contraindicated in patients with known hypersensitivity to DMF or any excipients in this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infection
Decreases in lymphocyte counts observed in patients treated with TECFIDERA 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 TECFIDERA 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 TECFIDERA should be considered until the infection(s) resolves.

Lymphopenia
TECFIDERA may decrease lymphocyte counts (see Section 4.8 Adverse effects (Undesirable effects)). In the MS placebo-controlled trials, mean lymphocyte counts decreased by approximately 30% during the first year of treatment with TECFIDERA and then remained stable. WBC counts $<3.0 \times 10^9$/L and lymphocyte counts $<0.5 \times 10^9$/L were reported in 6 to 7% of subjects given TECFIDERA. Prior to initiating treatment with TECFIDERA, a recent complete blood count (CBC) including lymphocytes (i.e. within 6 months) is recommended. A CBC, including lymphocytes, is also recommended, after 6 months of treatment and every 6 to 12 months thereafter, and as clinically indicated. In clinical studies, 9% of patients had lymphocyte counts $\geq 0.5 \times 10^9$/L and $<0.8 \times 10^9$/L for at least six months. 2% experienced lymphocyte counts $<0.5 \times 10^9$/L, for at least six months and in this group the majority of lymphocyte counts remained $<0.5 \times 10^9$/L with continued therapy. In controlled and uncontrolled clinical studies, the mean time for lymphocyte counts to return to normal after discontinuing TECFIDERA treatment was 4.7 weeks in patients without prolonged, severe lymphopenia and 29 weeks in patients with prolonged, severe lymphopenia (patients with lymphocyte counts $<0.5 \times 10^9$/L for six months or greater).

Consider interruption of TECFIDERA in patients with lymphocyte counts $<0.5 \times 10^9$/L persisting for more than six months. Lymphocytes counts should be followed until recovery. Assess the benefit/risk in patients who experience moderate lymphopenia for more than 6 months.

Interrupting treatment should be considered in patients with serious infections until the infection(s) resolved. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients.

Progressive Multifocal Leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) has occurred in the setting of lymphopenia ($<0.91 \times 10^9$/L) in patients with multiple sclerosis (MS) treated with TECFIDERA (see Section

4.8 Adverse effects (Undesirable effects)). These PML cases have occurred predominantly in the setting of prolonged moderate to severe lymphopenia. PML is an opportunistic viral infection of the brain that may lead to death or severe disability.

The symptoms of PML may be similar to a 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. At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation.

Anaphylactic reactions
Cases of anaphylaxis have been reported following TECFIDERA 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 TECFIDERA and seek immediate medical care if they experience signs or symptoms of anaphylaxis Treatment should not be restarted. (see Section 4.8 Adverse effects (Undesirable effects), Post-marketing experience).

Herpes Zoster Infections
Serious cases of herpes zoster have occurred with TECFIDERA, 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 TECFIDERA for signs and symptoms of herpes zoster. If herpes zoster occurs, appropriate treatment for herpes zoster should be administered. Consider withholding TECFIDERA treatment in patients with serious infections until the infection has resolved (see Section 4.8 Adverse effects (Undesirable effects), Post-marketing experience).

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

Use in renal impairment
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 TECFIDERA compared to patients that received placebo. The significance of these clinical observations is not known at this time.

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

The use of TECFIDERA 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 TECFIDERA is used in patients receiving chronic treatment with such medications.

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

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

Effects on laboratory tests
There are no data available on whether TECFIDERA interferes with laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In humans, TECFIDERA 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 (TECFIDERA). 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 TECFIDERA 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 TECFIDERA and did not alter the pharmacokinetic profile of TECFIDERA. Aspirin (non-enteric coated), 325 mg, when administered approximately 30 minutes before TECFIDERA, did not alter the pharmacokinetic profile of TECFIDERA.

Patients treated with TECFIDERA 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 TECFIDERA may receive non-live vaccines. No clinical data are available on the efficacy and safety of live attenuated vaccines in patients taking TECFIDERA.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Data from nonclinical studies do not suggest that TECFIDERA 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.

Use in pregnancy – Category B1
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.

The effects of TECFIDERA 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).

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

Use in lactation
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 TECFIDERA treatment. The benefit of breast-feeding for the child and the benefit of treatment for the woman should be taken into account.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

The most common adverse reactions (incidence ≥10% and >2% than placebo) for TECFIDERA 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 TECFIDERA were flushing (3%) and gastrointestinal events (4%).

In placebo-controlled and uncontrolled clinical studies, a total of 2513 patients have received TECFIDERA for periods up to 12 years and been followed for periods up to 13 years with an overall exposure equivalent to 11,318 person-years. A total of 1169 patients have received at least 5 years of treatment with TECFIDERA, and 426 patients have received at least 10 years of treatment with TECFIDERA. The experience in uncontrolled clinical trials is consistent with the experience in the placebo-controlled clinical trials.

In the two Phase 3 placebo-controlled trials, 1529 patients received TECFIDERA with an overall exposure of 2371 person-years (see Section 5.1 Pharmacodynamic properties, Clinical trials). The adverse reactions presented in the table below are based on safety information from 769 patients treated with TECFIDERA 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 TECFIDERA

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	Vomiting
	Nausea Abdominal Pain Upper Abdominal Pain	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 TECFIDERA 240 mg BID at ≥ 2% higher incidence than placebo

Primary System Organ Class Preferred Term	TECFIDERA 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	8	4
Rash	8	3
Erythema	5	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 Events

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 TECFIDERA 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 TECFIDERA (see Section 4.2 Dose and method of administration).

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 TECFIDERA compared with placebo. Four percent (4%) of patients treated with TECFIDERA 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 TECFIDERA.

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 TECFIDERA 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 TECFIDERA. Discontinuations due to elevated hepatic transaminases were <1% and similar in patients treated with TECFIDERA 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 Post marketing experience below).

Haematological

In the placebo-controlled studies, most patients (>98%) had normal lymphocyte values prior to initiating treatment. Upon treatment with TECFIDERA, 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 TECFIDERA. 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 TECFIDERA, 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.

Post-marketing experience

In post marketing experience, hypersensitivity reactions including urticaria, angioedema, and difficulty breathing have been reported following TECFIDERA administration. Cases of anaphylaxis have also been reported (see Section 4.4 Special warnings and precautions for use, Anaphylactic reactions).

Progressive multifocal leukoencephalopathy has occurred in the setting of lymphopenia ($<0.91 \times 10^9$/L) following TECFIDERA administration. These PML cases have occurred predominantly in the setting of prolonged moderate to severe lymphopenia. (see Section 4.4 Special warnings and precautions for use, Progressive Multifocal Leukoencephalopathy).

Liver function abnormalities (elevations in transaminases ≥ 3 times ULN with concomitant elevations in total bilirubin > 2 times ULN) have been reported following TECFIDERA 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 TECFIDERA, as clinically indicated.

Herpes zoster infection has been reported with TECFIDERA administration in post marketing experience. The majority of cases were non-serious (see Section 4.4 Special warnings and precautions for use, Herpes Zoster Infections). Other serious opportunistic infections have occurred with TECFIDERA, including cases of serious viral (herpes simplex virus, West Nile virus, cytomegalovirus), fungal (Candida and Aspergillus), and bacterial (Nocardia, Listeria monocytogenes, Mycobacterium tuberculosis) infections.

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

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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.

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.

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.

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.

Potential to prolong the QTc interval
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 trials
The efficacy and safety of TECFIDERA was demonstrated in three studies that evaluated TECFIDERA taken either twice or three times a day in patients with relapsing-remitting multiple sclerosis (RRMS).

The starting dose for TECFIDERA 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. Two of the three studies (Study 1 and Study 2) 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 TECFIDERA 240 mg twice a day (n=410), TECFIDERA 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 TECFIDERA 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. TECFIDERA 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 TECFIDERA 240 mg twice daily dose. The results for this study are shown in Table 3.

Table 3: Clinical and MRI Results of Study 1

	TECFIDERA 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)] Hazard ratio for first relapse (95% CI)	0.270 0.51 (0.40, 0.66)	0.461	<0.0001
Proportion with disability progression[(a)] Hazard ratio for progression (95% CI)	0.164 0.62 (0.44, 0.87)	0.271	0.0050
MRI Endpoint	n=152	n=165	
Number of new or newly enlarging T2 lesions over 2 years			

	TECFIDERA 240 mg BID (n=410)	Placebo (n=408)	P-value
Mean (median) Relative reduction (percentage) (95% CI)	3.2 (1.0) 85% (77%, 90%)	16.5 (7.0)	<0.0001
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) Relative reduction (percentage) (95% CI)	 2.0 (1.0) 72% (61%, 80%)	 5.7 (2.0)	< 0.0001
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 multicentre, 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 TECFIDERA 240 mg twice a day (n=359), TECFIDERA 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 treatment groups.

The annualised relapse rate was significantly lower in patients treated with TECFIDERA 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 confirmed disability progression defined as in Study 1.

TECFIDERA 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 this study are shown in Table 4.

Table 4: Clinical and MRI Results of Study 2

	TECFIDERA 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	17%	5%	14%
2 lesions	11%	3%	8%
3 lesions	8%	4%	6%
4 or more lesions	36%	76%	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%

	TECFIDERA 240 mg BID (n=359)	Placebo (n=363)	GA(n=350)
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 TECFIDERA versus placebo in all primary and secondary endpoints, including time to confirmed disability progression (32% relative reduction compared to placebo).

Study 3 (ENDORSE) enrolled eligible patients from Study 1 and 2 into an 8-year two phase extension study of 1736 patients with RRMS. The first phase was a multicentre, parallel group, randomised, dose blind, dose comparison study in which patients received TECFIDERA at a dose of 240 mg twice a day or 240 mg three times a day. The second phase was an open label study during which all patients received TECFIDERA at a dose of 240 mg twice a day. Eligible patients were enrolled at Week 96 (Visit 24) of their previous Study 1 or Study 2 visit, which served as the Baseline Visit for this extension study.

The primary objective of Study 3 was to evaluate the long-term safety of TECFIDERA. The secondary objectives were to evaluate the long-term efficacy of TECFIDERA using clinical endpoints (including relapse and ARR) and disability progression (EDSS) and on MS brain lesions on MRI scans.

The median age of patients was 40.0 years. Most patients (945 participants, 54%) were in the study for 7 years or longer and the median time spent in the study (min, max) was 6.759 (0.04, 10.98) years.

In the first year of treatment with TECFIDERA in Study 3, the adjusted ARR (95% CI) ranged from 0.125 (0.084, 0.188) to 0.183 (0.108, 0.308), and remained low in the eighth year, ranging from 0.077 (0.039, 0.153) to 0.129 (0.063, 0.265), in all treatment arms. During the overall study period, the adjusted ARR (95% CI) ranged from 0.126 (0.098, 0.162) to 0.185 (0.129, 0.265) and the majority of patients treated with TECFIDERA (between 59% and 69%) had no relapses.

The estimated proportion of relapse (95% CI), at 8 years (384 weeks), in Study 3 ranged from 0.414 (0.314, 0.531) to 0.502 (0.426, 0.584).

In an integrated analysis of Study 1 and Study 2 with Study 3, for patients continuously treated with TECFIDERA twice a day/twice a day (n = 501; patients treated with TECFIDERA 240 mg

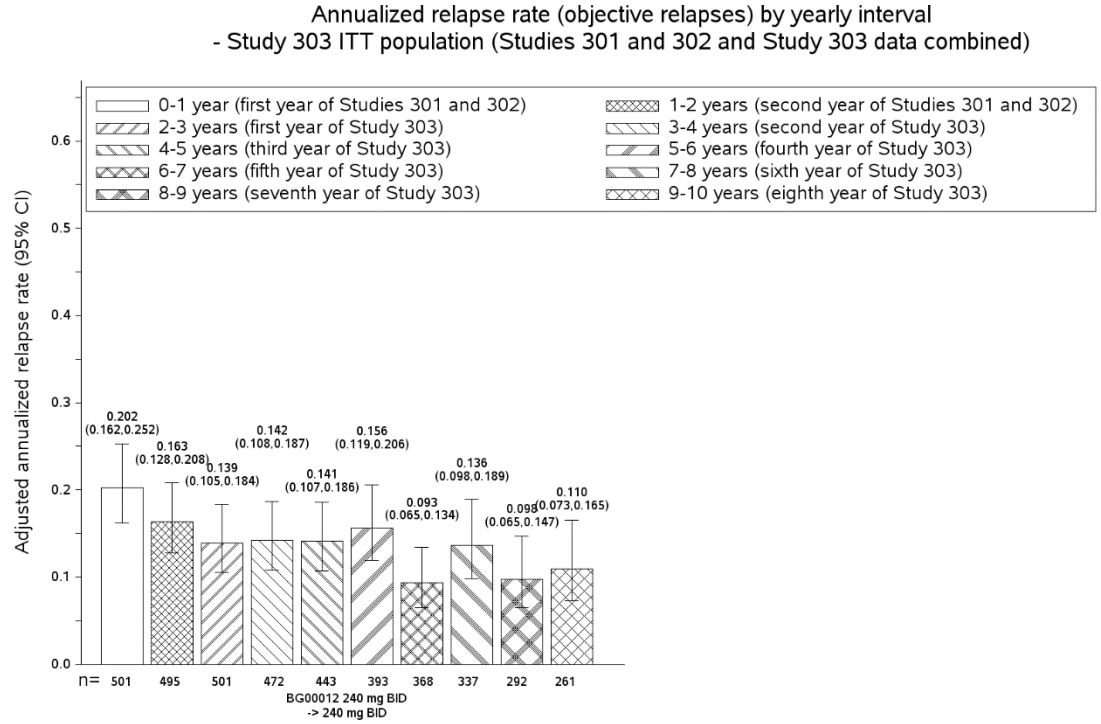
twice a day in Study 1 or 2 and then TECFIDERA 240 mg twice a day in study 3), adjusted ARR was 0.187 (95% CI, 0.156,0.224) in Study 1 and 2, and was 0.141 (95% CI, 0.119, 0.167) in Study 3. The data in Figure 1 demonstrates that the adjusted ARR in patients treated with TECFIDERA was steady throughout the treatment time in Study 1 or 2 and Study 3. For placebo/TECFIDERA patients (n = 249; patients treated with placebo in Study 1 or Study 2 and then switched to TECFIDERA in Study 3), adjusted ARR was 0.330 (95% CI, 0.266, 0.408) and decreased after initiating TECFIDERA, in Study 3, to 0.149 (95% CI, 0.116, 0.190), shown in Figure 2.

In Study 3, the mean (median) EDSS score at baseline ranged from 2.37 (2.0) to 2.64 (2.0). The estimated proportion of patients with confirmed progression (95% CI) in the eighth year of Study 3 after treatment with TECFIDERA ranged from 0.314 (0.268, 0.365) to 0.387 (0.311, 0.475).

In an integrated analysis of Study 1 and Study 2 with Study 3, at Week 480, the estimated proportion (95%) of patients with confirmed disability progression (Study 1, 2, and 3 data combined) was 0.349 (0.302, 0.401) in the TECFIDERA twice a day/twice a day group and 0.362 (0.292, 0.443) in the placebo/TECFIDERA group.

In Study 3, 752 patients were included in an MRI cohort, which included patients who had previously been included in the MRI cohort of Study 1 or Study 2. Due to sample size restrictions (by year 8 all groups has < 30 patients), MRI results are presented only through Year 6 of Study 3. Across all treatment arms, the adjusted mean number of new or newly enlarging T2 lesions relative to Study 3 baseline over 6 years ranged from 3.911 to 8.650 (the adjusted mean was based on negative binomial regression, adjusted for region and baseline volume of T2 lesions). The median number of new or newly enlarging T2 lesions over 6 years ranged from 1.0 to 3.0. Across all treatment arms, the mean (median) number of Gd+ lesions at 6 years ranged from 0.0 (0.0) to 0.7 (0.0). The percentage of patients with no Gd+ lesions ranged from 84% to 100%. The mean number of new T1 hypointense lesions over 6 years, adjusted for region and baseline volume of T1 lesions (based on negative binomial regression), ranged from 1.060 to 4.326. The median ranged from 1.0 to 2.5.

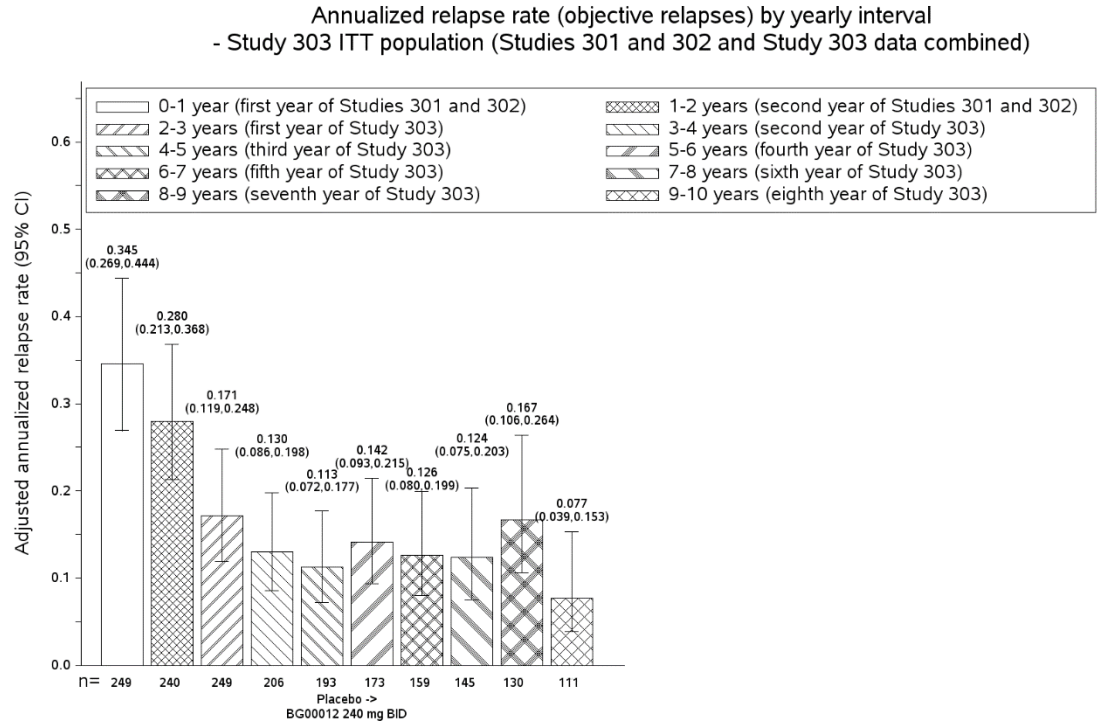
Figure 1: Annualized Adjusted Relapse Rate by Yearly Interval for Patients Treated Continuously with TECFIDERA Twice a Day / Twice a Day (Study 1, Study 2, and Study 3)



NOTE 1: Data after subjects switched to alternative MS medications during the period are excluded.
2: Adjusted annualized relapse rate and 95% CI are based on negative binomial regression, except for 4-5 years, 5-6 years, 6-7 years, 7-8 years, 8-9 years, and 9-10 years (third, fourth, fifth, sixth, seventh, and eighth years of Study 303), which are based on Poisson regression, adjusted for baseline EDSS (<=2.0 vs >2.0), baseline age (<40 vs >=40), region and number of relapses in the 1 year prior to 301/302 study entry.

SOURCE: BG12MS/109MS303/CSR/F-ARRP-INT.SAS DATE: 26FEB2020

Figure 2: Annualized Adjusted Relapse Rate by Yearly Interval for Placebo / TECFIDERA Twice a Day Patients (Study 1, Study 2, and Study 3)



NOTE 1: Data after subjects switched to alternative MS medications during the period are excluded.
2: Adjusted annualized relapse rate and 95% CI are based on negative binomial regression, except for 4-5 years, 5-6 years, 6-7 years, 7-8 years, 8-9 years, and 9-10 years (third, fourth, fifth, sixth, seventh, and eighth years of Study 303), which are based on Poisson regression, adjusted for baseline EDSS (<=2.0 vs >2.0), baseline age (<40 vs >=40), region and number of relapses in the 1 year prior to 301/302 study entry.

SOURCE: BG12MS/109MS303/CSR/F-ARRP-INT.SAS DATE: 26FEB2020

5.2 PHARMACOKINETIC PROPERTIES

Orally administered TECFIDERA 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 TECFIDERA. Therefore, all pharmacokinetic analyses related to TECFIDERA were performed with plasma MMF concentrations. Pharmacokinetic data were obtained in subjects with multiple sclerosis and healthy volunteers.

Absorption

The Tmax of TECFIDERA is 2-2.5 hours. As TECFIDERA 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 (Cmax) was 1.72 mg/L and overall (AUC) exposure was 8.02 h.mg/L in subjects with MS. Cmax 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 TECFIDERA. Therefore, TECFIDERA may be taken with or without food.

Distribution

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

Metabolism

In humans, TECFIDERA 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 14C-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 CO2 serving as a primary route of elimination.

Excretion
Exhalation of CO2 is the primary route of TECFIDERA 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 TECFIDERA at the therapeutic regimen.

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

Based on the results of ANOVA, body weight is the main covariate of exposure (by Cmax and AUC) in 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 Cmax and AUC.

Race and ethnicity have no effect on the pharmacokinetics of TECFIDERA.

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^{o}C. Store in original packaging in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

120 mg capsules:
Capsules are supplied in PVC/PE/PVDC aluminium blister packs, in pack sizes of 14 & 112*.

240 mg capsules:
Capsules are supplied in PVC/PE/PVDC aluminium blister packs, in pack sizes of 14* & 56.

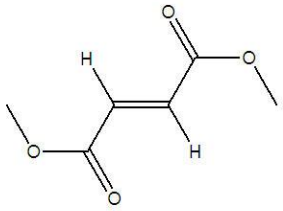
*Not all presentations are currently marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
The structural formula of DMF is shown below.



DMF is a white to off-white powder that is slightly soluble in water. It has a molecular formula of $C_6H_8O_4$ and a molecular weight of 144.13. The chemical name for DMF is dimethyl (2E)but-2-enedioate.

CAS number
The CAS Registry Number is 624-49-7.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

11 July 2013

10 DATE OF REVISION

28 June 2023

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Section 4.4	Addition of information relating to Lymphopenia.
Section 4.8	Updated to reflect long-term exposure data; additional information regarding lymphocyte recovery under Haematological.
Section 5.1	Updated to provide a summary of results from the long-term extension study 109MS303 (ENDORSE).