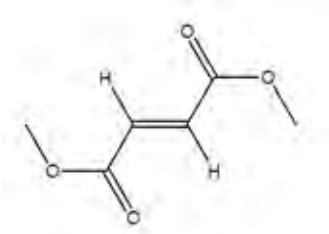
PRODUCT INFORMATION

TECFIDERA® (dimethyl fumarate [DMF])

NAME OF THE MEDICINE

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

The structural formula of DMF is shown below.



CAS registry number: 624-49-7

DESCRIPTION

DMF is a white to off-white powder that is slightly soluble in water. It has a molecular formula of C6H8O4 and a molecular weight of 144.13. The chemical name for DMF is dimethyl (2E)but-2-enedioate.

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).

PHARMACOLOGY

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.

Pharmacodynamics

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.

Pharmacokinetics
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 fecal 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 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 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.

CLINICAL TRIALS

The efficacy and safety of TECFIDERA was demonstrated in two 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. 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 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 1.

Table 1: 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			

	TECFIDERA 240 mg BID (n=410)	Placebo (n=408)	P-value
T2 lesions over 2 years			
Mean (median)	3.2 (1.0)	16.5 (7.0)	<0.0001
Relative reduction (percentage)	85%		
(95% CI)	(77%, 90%)		
Percentage of subjects with			
0 lesions	45%	27%	
1 lesion	17%	5%	
2 lesions	9%	2%	
3 lesions	7%	5%	
4 or more lesions	22%	61%	
Number of Gd lesions at 2 years			
Mean (median)	0.1 (0)	1.8 (0)	
Percentage of subjects with			
0 lesions	93%	62%	
1 lesion	5%	10%	
2 lesions	<1%	8%	
3 to 4 lesions	0	9%	
5 or more lesions	<1%	11%	
Relative odds reduction (percentage)	90%		<0.0001
(95% CI)	(78%, 95%)		
Number of new T1 hypointense lesions over 2 years			
Mean (median)	2.0 (1.0)	5.7 (2.0)	< 0.0001
Relative reduction (percentage)	72%		
(95% CI)	(61%, 80%)		
Percentage of subjects with			
0 lesions	40%	36%	
1 lesion	23%	10%	
2 lesions	10%	6%	
3 to 4 lesions	17%	12%	
5 or more lesions	9%	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 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 labeling. The results for this study are shown in Table 2.

Table 2: 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			

	TECFIDERA 240 mg BID (n=359)	Placebo (n=363)	GA (n=350)
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%
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).

INDICATIONS

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

CONTRAINDICATIONS

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

PRECAUTIONS

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 ADVERSE 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) (i.e. within 6 months) is recommended. A CBC is recommended annually, and as clinically indicated. Interrupting treatment should be considered in patients with serious infections until the infection(s) resolves. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients.

Vaccination: 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. The efficacy of vaccines administered during treatment with TECFIDERA has not been evaluated in clinical trials.

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 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.

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 fetal weight and caused minor impairment of ossification in fetuses, concomitant with maternal toxicity; the no-effect dose for fetal 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 embryofetal 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 fetus.

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.

Paediatric use

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

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.

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.

Effect on Laboratory Tests

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

INTERACTIONS WITH OTHER MEDICINES

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.

Commonly used drugs in patients with multiple sclerosis, intramuscular (IM) interferon beta-a 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.

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.

ADVERSE EFFECTS

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 2468 patients have received TECFIDERA 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 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 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 3: 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 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 4: 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.

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 DOSAGE AND ADMINISTRATION).*

Gastrointestinal
The incidence of patients with GI events (e.g. nausea, vomiting, diarrhea, 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. There were no elevations in transaminases ≥ 3 times ULN with concomitant elevations in total bilirubin > 2 times ULN. Discontinuations due to elevated hepatic transaminases were <1% and similar in patients treated with TECFIDERA or placebo.

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. 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.

DOSAGE AND 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 microtablets 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 INTERACTIONS WITH OTHER MEDICINES).*

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

OVERDOSAGE

No cases of overdose have been reported to date. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

120 mg capsule:
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.

Capsules are supplied in PVC/PE/PVDC aluminium blister packs, in pack sizes of 14 & 112.

240 mg capsule:
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.

Capsules are supplied in PVC/PE/PVDC aluminium blister packs, in pack sizes of 12 & 56.

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

NAME AND ADDRESS OF THE SPONSOR

Biogen Idec Australia Pty Ltd
ABN 30 095 760 115
Suite 1, Level 5, 123 Epping Road
North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION ON THE ARTG

11 July 2013

DATE OF MOST RECENT AMENDMENT

21 August 2013