

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Tecfidera 120 mg gastro-resistant hard capsules  
Tecfidera 240 mg gastro-resistant hard capsules

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Tecfidera 120mg gastro-resistant hard capsules

Each gastro-resistant hard capsule contains 120 mg dimethyl fumarate.

Tecfidera 240mg gastro-resistant hard capsules

Each gastro-resistant hard capsule contains 240 mg dimethyl fumarate

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Gastro-resistant hard capsule

Tecfidera 120mg gastro-resistant hard capsules

Green and white gastro-resistant hard capsules, size 0, printed with 'BG-12 120 mg' containing microtablets.

Tecfidera 240mg gastro-resistant hard capsules

Green gastro-resistant hard capsules, size 0, printed with 'BG-12 240 mg' containing microtablets.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Tecfidera is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (see section 5.1 for important information on the populations for which efficacy has been established).

### **4.2 Posology and method of administration**

Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis.

#### Posology

The starting dose is 120 mg twice a day. After 7 days, the dose should be increased to the recommended maintenance dose of 240 mg twice a day (see section 4.4).

If a patient misses a dose, a double dose should not be taken. The patient may take the missed dose only if they leave 4 hours between doses. Otherwise the patient should wait until the next scheduled dose.

Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and

gastrointestinal adverse reactions. Within 1 month, the recommended maintenance dose of 240 mg twice a day should be resumed.

Tecfidera should be taken with food (see section 5.2). For those patients who may experience flushing or gastrointestinal adverse reactions, taking Tecfidera with food may improve tolerability (see sections 4.4, 4.5 and 4.8).

#### *Special populations*

##### *Elderly*

Clinical studies of Tecfidera had limited exposure to patients aged 55 years and above, and did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients (see section 5.2). Based on the mode of action of the active substance there are no theoretical reasons for any requirement for dose adjustments in the elderly.

##### *Renal and hepatic impairment*

Tecfidera has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology studies, no dose adjustments are needed (see section 5.2). Caution should be used when treating patients with severe renal or severe hepatic impairment (see section 4.4).

##### *Paediatric population*

The safety and efficacy of Tecfidera in children and adolescents aged 10 to 18 years have not yet been established.

Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made. There is no relevant use of Tecfidera in children aged less than 10 years for the indication of relapsing remitting multiple sclerosis.

#### Method of administration

For oral use.

The capsule should be swallowed whole. The capsule or its contents should not be crushed, divided, dissolved, sucked or chewed as the enteric-coating of the microtablets prevents irritant effects on the gut.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Blood/laboratory tests

Changes in renal laboratory tests have been seen in clinical trials in subjects treated with dimethyl fumarate (see section 4.8). The clinical implications of these changes are unknown. Assessment of renal function (e.g. creatinine, blood urea nitrogen and urinalysis) is recommended prior to treatment initiation, after 3 and 6 months of treatment, every 6 to 12 months thereafter and as clinically indicated.

Drug-induced liver injury, including liver enzyme increase ( $\geq 3$  upper limit of normal (ULN)) and elevation of total bilirubin levels ( $\geq 2$  ULN) can result from treatment with dimethyl fumarate. The time to onset can be directly, several weeks or longer. Resolution of the adverse reactions has been observed after treatment was discontinued. Assessment of serum aminotransferases (e.g. alanine aminotransferase (ALT), aspartate aminotransferase (AST)) and total bilirubin levels are recommended prior to treatment initiation and during treatment as clinically indicated.

Patients treated with Tecfidera may develop severe prolonged lymphopenia (see section 4.8). Dimethyl fumarate has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients. Prior to initiating treatment with Tecfidera, a current complete blood count, including lymphocytes, must be performed. If lymphocyte count is found to be below the normal range, thorough assessment of possible causes should be completed prior to initiation of treatment with Tecfidera.

After starting therapy, complete blood counts, including lymphocytes, must be performed every 3 months.

Interruption of Tecfidera should be considered in patients with lymphocyte counts  $<0.5 \times 10^9/L$  persisting for more than 6 months. The benefit/risk balance of the therapy should be reconsidered in discussion with the patient in the context of other therapeutic options available. Clinical factors, evaluation of any laboratory and imaging investigations could be included as part of this re-consideration. If treatment is continued despite a persistent lymphocyte count  $< 0.5 \times 10^9/L$ , enhanced vigilance is recommended (see also subsection on PML). Lymphocyte counts should be followed until recovery. Upon recovery and in the absence of alternative treatment options, decisions about whether or not to restart Tecfidera after treatment discontinuation should be based on clinical judgement.

The benefit/risk in patients with lymphocyte counts  $\geq 0.5 \times 10^9/L$  and  $< 0.8 \times 10^9/L$  for more than six months should be assessed.

#### Magnetic Resonance imaging (MRI)

Before initiating treatment with Tecfidera, a baseline MRI should be available (usually within 3 months) as a reference. The need for further MRI scanning should be considered in accordance with national and local recommendations. MRI imaging may be considered as part of increased vigilance in patients considered at increased risk of PML. In case of clinical suspicion of PML, MRI should be performed immediately for diagnostic purposes.

#### Progressive Multifocal Leukoencephalopathy (PML)

PML cases have occurred with dimethyl fumarate and other medicinal products containing fumarates in the setting of moderate to severe prolonged lymphopenia. PML is an opportunistic infection caused by John-Cunningham virus (JCV), which may be fatal or result in severe disability. PML can only occur in the presence of a JCV infection. If JCV testing is undertaken, it should be considered that the influence of lymphopenia on the accuracy of anti-JCV antibody test 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.

At the first sign or symptom suggestive of PML, Tecfidera should be withheld and appropriate diagnostic evaluations 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.

#### Prior treatment with immunosuppressive or immunomodulating therapies

No studies have been performed evaluating the efficacy and safety of Tecfidera when switching patients from other disease modifying therapies to Tecfidera. The contribution of prior immunosuppressive therapy to the development of PML in dimethyl fumarate treated patients is unknown. When switching patients from another disease modifying therapy to Tecfidera, the half-life and mode of action of the other therapy should be considered in order to avoid an additive immune effect while at the same time, reducing the risk of reactivation of MS.

A complete blood count is recommended prior to initiating Tecfidera and regularly during treatment (see Blood/laboratory tests above).

Tecfidera can generally be started immediately after discontinuation of interferon or glatiramer acetate.

#### Severe renal and hepatic impairment

Tecfidera has not been studied in patients with severe renal or severe hepatic impairment and caution should, therefore, be used in these patients (see section 4.2).

#### Severe active gastrointestinal disease

Tecfidera has not been studied in patients with severe active gastrointestinal disease and caution should, therefore, be used in these patients.

#### Flushing

In clinical trials, 34% of Tecfidera treated patients experienced flushing. In the majority of patients who experienced flushing, it was mild or moderate in severity. Data from healthy volunteer studies suggest that dimethyl fumarate-associated flushing is likely to be prostaglandin mediated. A short course of treatment with 75 mg non-enteric coated acetylsalicylic acid may be beneficial in patients affected by intolerable flushing (see section 4.5). In two healthy volunteer studies, the occurrence and severity of flushing over the dosing period was reduced.

In clinical trials, 3 patients out of a total of 2,560 patients treated with dimethyl fumarate experienced serious flushing symptoms that were probable hypersensitivity or anaphylactoid reactions. These events were not life-threatening, but led to hospitalisation. Prescribers and patients should be alert to this possibility in the event of severe flushing reactions (see sections 4.2, 4.5 and 4.8).

#### Anaphylactic reactions

Cases of anaphylaxis/anaphylactoid reaction have been reported following Tecfidera administration in the post-marketing setting. Symptoms may include dyspnoea, hypoxia, hypotension, angioedema, rash or urticaria. The mechanism of dimethyl fumarate induced anaphylaxis is unknown. Reactions generally occur after the first dose, but may also 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).

#### Infections

In phase III placebo-controlled studies, the incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with Tecfidera or placebo, respectively. However, due to Tecfidera immunomodulatory properties (see section 5.1), if a patient develops a serious infection, suspending treatment with Tecfidera should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Patients receiving Tecfidera should be instructed to report symptoms of infections to a physician. Patients with serious infections should not start treatment with Tecfidera until the infection(s) is resolved.

There was no increased incidence of serious infections observed in patients with lymphocyte counts  $<0.8 \times 10^9/L$  or  $<0.5 \times 10^9/L$  (see Section 4.8). If therapy is continued in the presence of moderate to severe prolonged lymphopenia, the risk of an opportunistic infection, including PML, cannot be ruled out (see section 4.4 subsection PML).

#### Herpes zoster infections

Cases of herpes zoster have occurred with Tecfidera. The majority of cases were non-serious, however, serious cases, including disseminated herpes zoster, herpes zoster ophthalmicus, herpes zoster oticus, herpes zoster infection neurological, herpes zoster meningoencephalitis and herpes

zoster meningomyelitis have been reported. These events may occur at any time during treatment. Monitor patients taking Tecfidera for signs and symptoms of herpes zoster especially when concurrent lymphocytopenia is reported. 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).

#### Treatment initiation

Tecfidera treatment should be started gradually to reduce the occurrence of flushing and gastrointestinal adverse reactions (see section 4.2).

#### Fanconi syndrome

Cases of Fanconi syndrome have been reported for a medicinal product containing dimethyl fumarate in combination with other fumaric acid esters. Early diagnosis of Fanconi syndrome and discontinuation of dimethyl fumarate treatment are important to prevent the onset of renal impairment and osteomalacia, as the syndrome is usually reversible. The most important signs are: proteinuria, glucosuria (with normal blood sugar levels), hyperaminoaciduria and phosphaturia (possibly concurrent with hypophosphatemia). Progression might involve symptoms such as polyuria, polydipsia and proximal muscle weakness. In rare cases hypophosphataemic osteomalacia with non-localised bone pain, elevated alkaline phosphatase in serum and stress fractures may occur. Importantly, Fanconi syndrome can occur without elevated creatinine levels or low glomerular filtration rate. In case of unclear symptoms Fanconi syndrome should be considered and appropriate examinations should be performed.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Tecfidera has not been studied in combination with anti-neoplastic or immunosuppressive therapies and caution should, therefore, be used during concomitant administration. In multiple sclerosis clinical studies, the concomitant treatment of relapses with a short course of intravenous corticosteroids was not associated with a clinically relevant increase of infection.

Concomitant administration of non-live vaccines according to national vaccination schedules may be considered during Tecfidera therapy. In a clinical study involving a total of 71 patients with relapsing remitting multiple sclerosis, patients on Tecfidera 240 mg twice daily for at least 6 months (n=38) or non-pegylated interferon for at least 3 months (n=33), mounted a comparable immune response (defined as  $\geq 2$ -fold increase from pre- to post-vaccination titer) to tetanus toxoid (recall antigen) and a conjugated meningococcal C polysaccharide vaccine (neoantigen), while the immune response to different serotypes of an unconjugated 23-valent pneumococcal polysaccharide vaccine (T-cell independent antigen) varied in both treatment groups. A positive immune response defined as a  $\geq 4$ -fold increase in antibody titer to the three vaccines, was achieved by fewer subjects in both treatment groups. Small numerical differences in the response to tetanus toxoid and pneumococcal serotype 3 polysaccharide were noted in favour of non-pegylated interferon.

No clinical data are available on the efficacy and safety of live attenuated vaccines in patients taking Tecfidera. Live vaccines might carry an increased risk of clinical infection and should not be given to patients treated with Tecfidera unless, in exceptional cases, this potential risk is considered to be outweighed by the risk to the individual of not vaccinating.

During treatment with Tecfidera, simultaneous use of other fumaric acid derivatives (topical or systemic) should be avoided.

In humans, dimethyl fumarate is extensively metabolised by esterases before it reaches the systemic circulation and further metabolism occurs through the tricarboxylic acid 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 dimethyl fumarate and monomethyl fumarate (a primary metabolite of dimethyl fumarate).

Commonly used medicinal products in patients with multiple sclerosis, intramuscular interferon beta-1a and glatiramer acetate, were clinically tested for potential interactions with dimethyl fumarate and did not alter the pharmacokinetic profile of dimethyl fumarate.

Evidence from healthy volunteer studies suggests that Tecfidera-associated flushing is likely to be prostaglandin mediated. In two healthy volunteer studies, the administration of 325 mg (or equivalent) non-enteric coated acetylsalicylic acid, 30 minutes prior to Tecfidera, dosing over 4 days and over 4 weeks, respectively, did not alter the pharmacokinetic profile of Tecfidera. Potential risks associated with acetylsalicylic acid therapy should be considered prior to co-administration with Tecfidera in patients with Relapsing Remitting MS. Long term (> 4 weeks) continuous use of acetylsalicylic acid has not been studied (see sections 4.4 and 4.8).

Concurrent therapy with nephrotoxic medicinal products (such as aminoglycosides, diuretics, non-steroidal anti-inflammatory drugs or lithium) may increase the potential of renal adverse reactions (e.g. proteinuria see section 4.8) in patients taking Tecfidera (see section 4.4 Blood/laboratory tests).

Consumption of moderate amounts of alcohol did not alter exposure to dimethyl fumarate and was not associated with an increase in adverse reactions. Consumption of large quantities of strong alcoholic drinks (more than 30% alcohol by volume) should be avoided within an hour of taking Tecfidera, as alcohol may lead to increased frequency of gastrointestinal adverse reactions.

*In vitro* CYP induction studies did not demonstrate an interaction between Tecfidera and oral contraceptives. In an *in vivo* study, co-administration of Tecfidera with a combined oral contraceptive (norgestimate and ethinyl estradiol) did not elicit any relevant change in oral contraceptive exposure. No interaction studies have been performed with oral contraceptives containing other progestogens, however an effect of Tecfidera on their exposure is not expected.

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no or limited amount of data from the use of dimethyl fumarate in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Tecfidera is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception (see section 4.5). Tecfidera 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 unknown whether dimethyl fumarate or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Tecfidera therapy. The benefit of breast-feeding for the child and the benefit of therapy for the woman should be taken into account.

#### Fertility

There are no data on the effects of dimethyl fumarate on human fertility. Data from preclinical studies do not suggest that dimethyl fumarate would be associated with an increased risk of reduced fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Tecfidera has no or negligible influence on the ability to drive and use machines. No studies on the ability to drive and use machines have been conducted but no effects potentially influencing this ability were found to be related to dimethyl fumarate in clinical studies.

## 4.8 Undesirable effects

### Summary of the safety profile

The most common adverse reactions (incidence  $\geq 10\%$ ) for patients treated with dimethyl fumarate were flushing and gastrointestinal events (i.e. diarrhoea, nausea, abdominal pain, abdominal pain upper). Flushing and gastrointestinal events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience flushing and gastrointestinal events, these events may continue to occur intermittently throughout treatment with Tecfidera. The most commonly reported adverse reactions 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 2,468 patients have received Tecfidera and been followed for periods up to 4 years with an overall exposure equivalent to 3,588 person-years. Approximately 1,056 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.

### Tabulated summary of adverse reactions

Adverse reactions, which were more frequently reported in Tecfidera versus placebo-treated patients, are presented in the table below. These data were derived from 2 pivotal Phase 3 placebo-controlled, double-blind clinical trials with a total of 1,529 patients treated with Tecfidera and for up to 24 months with an overall exposure of 2,371 person-years (see section 5.1). The frequencies described in the table below are based on 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 are expressed according to the following categories:

- Very common ( $\geq 1/10$ )
- Common ( $\geq 1/100$  to  $<1/10$ )
- Uncommon ( $\geq 1/1,000$  to  $<1/100$ )
- Rare ( $\geq 1/10,000$  to  $<1/1,000$ )
- Very rare ( $<1/10,000$ )
- Not known (frequency cannot be estimated from the available data)

MedDRA System Organ Class	Adverse reaction	Frequency category
Infections and infestations	Gastroenteritis	Common
	Progressive multifocal leukoencephalopathy (PML) <sup>1</sup>	Not known
	Herpes zoster <sup>1</sup>	Not known
Blood and lymphatic system disorders	Lymphopenia	Common
	Leucopenia	Common
	Thrombocytopenia	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylaxis <sup>1</sup>	Not known
	Dyspnoea <sup>1</sup>	Not known
	Hypoxia <sup>1</sup>	Not known
	Hypotension <sup>1</sup>	Not known
	Angioedema <sup>1</sup>	Not known



<b>MedDRA System Organ Class</b>	<b>Adverse reaction</b>	<b>Frequency category</b>
Nervous system disorders	Burning sensation	Common
Vascular disorders	Flushing	Very common
	Hot flush	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Nausea	Very common
	Abdominal pain upper	Very common
	Abdominal pain	Very common
	Vomiting	Common
	Dyspepsia	Common
	Gastritis	Common
	Gastrointestinal disorder	Common
Hepatobiliary disorders	Aspartate aminotransferase increased	Common
	Alanine aminotransferase increased	Common
	Drug-induced liver injury <sup>1</sup>	Not known
Skin and subcutaneous tissue disorders	Pruritus	Common
	Rash	Common
	Erythema	Common
Renal and urinary disorders	Proteinuria	Common
General disorders and administration site conditions	Feeling hot	Common
Investigations	Ketones measured in urine	Very common
	Albumin urine present	Common
	White blood cell count decreased	Common

<sup>1</sup>Adverse reactions derived only during post marketing experience

#### Description of selected adverse reactions

##### *Flushing*

In the placebo-controlled studies, the incidence of flushing (34% versus 4%) and hot flush (7% versus 2%) was increased in patients treated with Tecfidera compared to placebo, respectively. Flushing is usually described as flushing or hot flush, but can include other events (e.g. warmth, redness, itching, and burning sensation). Flushing events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience flushing, these events may continue to occur intermittently throughout treatment with Tecfidera. 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 sections 4.2, 4.4 and 4.5).

### *Gastrointestinal*

The incidence of gastrointestinal events (e.g. diarrhoea [14% versus 10%], nausea [12% versus 9%], upper abdominal pain [10% versus 6%], abdominal pain [9% versus 4%], vomiting [8% versus 5%] and dyspepsia [5% versus 3%]) was increased in patients treated with Tecfidera compared to placebo, respectively. Gastrointestinal events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience gastrointestinal events, these events may continue to occur intermittently throughout treatment with Tecfidera. In the majority of patients who experienced gastrointestinal events, it was mild or moderate in severity. Four per cent (4%) of patients treated with Tecfidera discontinued due to gastrointestinal events. The incidence of serious gastrointestinal events, including gastroenteritis and gastritis, was seen in 1% of patients treated with Tecfidera (see section 4.2).

### *Hepatic function*

Based on data from placebo-controlled studies, 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  $\geq 3$  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  $\geq 3$  times ULN with concomitant elevations in total bilirubin >2 times ULN, were not observed in placebo-controlled studies.

Increase of liver enzymes and cases of drug-induced liver injury (elevations in transaminases  $\geq 3$  times ULN with concomitant elevations in total bilirubin >2 times ULN), have been reported in post marketing experience following Tecfidera administration, which resolved upon treatment discontinuation.

### *Infections*

Herpes zoster infections have been reported with Tecfidera use. In an ongoing long-term extension study, in which 1736 MS patients are treated with Tecfidera, approximately 5% experienced one or more events of herpes zoster, the majority of which were mild to moderate in severity. Most subjects, including those who experienced a serious herpes zoster infection, had lymphocyte counts above the lower limit of normal. Grade 2 and 3 lymphopenia prevailed in subjects with concurrent lymphocytopenia. In the post-marketing setting most cases of herpes zoster infection were non-serious and resolved with treatment. Limited data is available on ALC in patients with herpes zoster infection in the post-marketing setting. However, when reported, most patients experienced grade 2 ( $< 0.8 \times 10^9/L$  to  $0.5 \times 10^9/L$ ) or grade 3 ( $< 0.5 \times 10^9/L$  to  $0.2 \times 10^9/L$ ) lymphopenia (see section 4.4).

### *Lymphopenia*

In the placebo-controlled studies most patients (>98%) had normal lymphocyte values prior to initiating treatment. Upon treatment with Tecfidera, mean lymphocyte 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. Lymphocyte counts  $< 0.5 \times 10^9/L$  were observed in <1% of patients treated with placebo and 6% of patients treated with Tecfidera. A lymphocyte count  $< 0.2 \times 10^9/L$  was observed in 1 patient treated with Tecfidera and in no patients treated with placebo.

In clinical studies (both controlled and uncontrolled), 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% of patients 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.

PML has occurred in the setting of moderate to severe prolonged lymphopenia (see section 4.4).

#### *Laboratory abnormalities*

In the placebo-controlled studies, measurement of urinary ketones (1+ or greater) was higher in patients treated with Tecfidera (45%) compared to placebo (10%). No untoward clinical consequences were observed in clinical trials.

Levels of 1,25-dihydroxyvitamin D decreased in Tecfidera treated patients relative to placebo (median percentage decrease from baseline at 2 years of 25% versus 15%, respectively) and levels of parathyroid hormone (PTH) increased in Tecfidera treated patients relative to placebo (median percentage increase from baseline at 2 years of 29% versus 15%, respectively). Mean values for both parameters remained within normal range.

A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.

#### Paediatric population

The safety of Tecfidera in paediatric patients with multiple sclerosis below the age of 18 has not yet been established. In a small 24-week open-label uncontrolled study in paediatric patients with RRMS aged 13 to 17 years (120 mg twice a day for 7 days followed by 240 mg twice a day for the remainder of treatment; safety population, n=22), followed by a 96 week extension study (240mg twice per day ; safety population n=20), the safety profile appeared similar to that observed in adult patients.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via **the national reporting system listed in Appendix V**.

### **4.9 Overdose**

Cases of overdose with Tecfidera have been reported. The symptoms described in these cases were consistent with the known adverse reaction profile of Tecfidera. 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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, ATC code: L04AX07

#### Mechanism of action

The mechanism by which dimethyl fumarate exerts therapeutic effects in multiple sclerosis is not fully understood. Preclinical studies indicate that dimethyl fumarate pharmacodynamic responses appear to be primarily mediated through activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway. Dimethyl fumarate has been shown to up regulate Nrf2-dependent antioxidant genes in patients (e.g. NAD(P)H dehydrogenase, quinone 1; [NQO1]).

#### Pharmacodynamic effects

##### *Effects on the immune system*

In preclinical and clinical studies, dimethyl fumarate demonstrated anti-inflammatory and

immunomodulatory properties. Dimethyl fumarate and monomethyl fumarate, the primary metabolite of dimethyl fumarate, significantly reduced immune cell activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli in preclinical models. In clinical studies with psoriasis patients, dimethyl fumarate affected lymphocyte phenotypes through a down-regulation of pro-inflammatory cytokine profiles (T<sub>H</sub>1, T<sub>H</sub>17), and biased towards anti-inflammatory production (T<sub>H</sub>2). Dimethyl fumarate demonstrated therapeutic activity in multiple models of inflammatory and neuroinflammatory injury. In Phase 3 studies in MS patients, upon treatment with Tecfidera mean lymphocyte counts decreased on average by approximately 30% of their baseline value over the first year with a subsequent plateau.

### Clinical efficacy and safety

Two, 2-year, randomised, double-blind, placebo controlled studies [Study 1 (DEFINE) with 1234 subjects and Study 2 (CONFIRM) with 1417 subjects] of subjects with relapsing-remitting multiple sclerosis (RRMS) were performed. Subjects with progressive forms of MS were not included in these studies. Efficacy (see table below) and safety were demonstrated in subjects with Expanded Disability Status Scale (EDSS) scores ranging from 0 to 5 inclusive, who had experienced at least 1 relapse during the year prior to randomisation, or, in the 6 weeks before randomisation had a brain Magnetic Resonance Imaging (MRI) demonstrating at least one gadolinium-enhancing (Gd+) lesion. Study 2 contained a rater-blinded (i.e. study physician/ investigator assessing the response to study treatment was blinded) reference comparator of glatiramer acetate.

In Study 1, patients had the following median baseline characteristics: age 39 years, disease duration 7.0 years, EDSS score 2.0. In addition, 16% of patients had an EDSS score >3.5, 28% had ≥2 relapses in the prior year and 42% had previously received other approved MS treatments. In the MRI cohort 36% of patients entering the study had Gd+ lesions at baseline (mean number of Gd+ lesions 1.4).

In Study 2, patients had the following median baseline characteristics: age 37 years, disease duration 6.0 years, EDSS score 2.5. In addition, 17% of patients had an EDSS score >3.5, 32% had ≥2 relapses in the prior year and 30% had previously received other approved MS treatments. In the MRI cohort 45% of patients entering the study had Gd+ lesions at baseline (mean number of Gd+ lesions 2.4).

Compared to placebo, subjects treated with Tecfidera had a clinically meaningful and statistically significant reduction on: the primary endpoint in Study 1, proportion of subjects relapsed at 2 years; and the primary endpoint in Study 2, annualised relapse rate at 2 years.

The annualised relapse rate for glatiramer acetate and placebo was 0.286 and 0.401 respectively in Study 2, corresponding to a reduction of 29% (p=0.013), which is consistent with approved prescribing information.

	DEFINE		CONFIRM		
	Placebo	Tecfidera 240 mg twice a day	Placebo	Tecfidera 240 mg twice a day	Glatiramer acetate
<b>Clinical Endpoints<sup>a</sup></b>					
No. subjects	408	410	363	359	350
Annualised relapse rate	0.364	0.172***	0.401	0.224***	0.286*
Rate ratio (95% CI)		0.47 (0.37, 0.61)		0.56 (0.42, 0.74)	0.71 (0.55, 0.93)
Proportion relapsed	0.461	0.270***	0.410	0.291**	0.321**
Hazard ratio (95% CI)		0.51 (0.40, 0.66)		0.66 (0.51, 0.86)	0.71 (0.55, 0.92)
Proportion with 12-week confirmed disability progression	0.271	0.164**	0.169	0.128 <sup>#</sup>	0.156 <sup>#</sup>

	DEFINE		CONFIRM		
	Placebo	Tecfidera 240 mg twice a day	Placebo	Tecfidera 240 mg twice a day	Glatiramer acetate
Hazard ratio (95% CI)		0.62 (0.44, 0.87)		0.79 (0.52, 1.19)	0.93 (0.63, 1.37)
Proportion with 24 week confirmed disability progression	0.169	0.128#	0.125	0.078#	0.108#
Hazard ratio (95% CI)		0.77 (0.52, 1.14)		0.62 (0.37, 1.03)	0.87 (0.55, 1.38)
<b>MRI Endpoints<sup>b</sup></b>					
No. subjects	165	152	144	147	161
Mean (median) number of new or newly enlarging T2 lesions over 2 years	16.5 (7.0)	3.2 (1.0)***	19.9 (11.0)	5.7 (2.0)***	9.6 (3.0)***
Lesion mean ratio (95% CI)		0.15 (0.10, 0.23)		0.29 (0.21, 0.41)	0.46 (0.33, 0.63)
Mean (median) number of Gd lesions at 2 years	1.8 (0)	0.1 (0)***	2.0 (0.0)	0.5 (0.0)***	0.7 (0.0)**
Odds ratio (95% CI)		0.10 (0.05, 0.22)		0.26 (0.15, 0.46)	0.39 (0.24, 0.65)
Mean (median) number of new T1 hypointense lesions over 2 years	5.7 (2.0)	2.0 (1.0)***	8.1 (4.0)	3.8 (1.0)***	4.5 (2.0)**
Lesion mean ratio (95% CI)		0.28 (0.20, 0.39)		0.43 (0.30, 0.61)	0.59 (0.42, 0.82)

<sup>a</sup>All analyses of clinical endpoints were intent-to-treat; <sup>b</sup>MRI analysis used MRI cohort  
\*P-value < 0.05; \*\*P-value < 0.01; \*\*\*P-value < 0.0001; #not statistically significant

#### Efficacy in patients with high disease activity:

Consistent treatment effect on relapses in a subgroup of patients with high disease activity was observed, whilst the effect on time to 3-month sustained disability progression was not clearly established. Due to the design of the studies, high disease activity was defined as follows:

- Patients with 2 or more relapses in one year, and with one or more Gd-enhancing lesions on brain MRI (n=42 in DEFINE; n=51 in CONFIRM) or,
- Patients who have failed to respond to a full and adequate course (at least one year of treatment) of beta-interferon, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or patients having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years (n=177 in DEFINE; n=141 in CONFIRM).

#### Paediatric population

Tecfidera was evaluated in a prospective open-label, uncontrolled study in 22 paediatric patients with RRMS aged 13 to 17 years (4 patients aged ≤14 years). Subjects received Tecfidera 120 mg twice a day for 7 days followed by 240 mg twice a day for 24 weeks. The median number of new or newly enlarging T2 hyperintense lesions changed from 2 in the 8 week pre-treatment evaluation period to 0 in the final 8 weeks of the treatment period (median change -2, n=16). Patients subsequently entered an extension study for a further 96 weeks. Among the 10 patients with MRI data between weeks 64 and week 72 of the extension study, the median number of subjects with new or newly enlarging T2 hyperintense lesions was 0 (range 0,2). Over the full treatment period (120-week), ARR was 0.2 representing an 84.5% relative reduction in relapses (n=20; 95% CI [66.8, 92.8], p<0.0001), when compared to the year prior to treatment initiation. These data should be considered cautiously regarding limitations of the study design (no control arm, pre- versus post-dose comparison) (see section 4.2).

## 5.2 Pharmacokinetic properties

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

### Absorption

The  $T_{max}$  of monomethyl fumarate is 2 to 2.5 hours. As Tecfidera gastro-resistant hard capsules contain microtablets, which are protected by an enteric coating, absorption does not commence until they leave the stomach (generally less than 1 hour). Following 240 mg twice a day administered with food, the median peak ( $C_{max}$ ) was 1.72 mg/l and overall area under the curve (AUC) exposure was 8.02 h.mg/l in subjects with multiple sclerosis. Overall,  $C_{max}$  and AUC increased approximately dose-proportionally in the dose range studied (120 mg to 360 mg). In subjects with multiple sclerosis, two 240 mg doses were administered 4 hours apart as part of a three times a day dosing regimen. This resulted in a minimal accumulation of exposure yielding an increase in the median  $C_{max}$  of 12% compared to the twice daily dosing (1.72 mg/l for twice daily compared to 1.93 mg/l for three times daily) with no safety implications.

Food does not have a clinically significant effect on exposure of dimethyl fumarate. However, Tecfidera should be taken with food due to improved tolerability with respect to flushing or gastrointestinal adverse events (see section 4.2).

### Distribution

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

### Biotransformation

In humans, dimethyl fumarate is extensively metabolised with less than 0.1% of the dose excreted as unchanged dimethyl fumarate in urine. It is initially 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 cycle, with no involvement of the cytochrome P450 (CYP) system. A single 240 mg  $^{14}C$ -dimethyl fumarate dose study identified glucose as the predominant metabolite in human plasma. Other circulating metabolites included fumaric acid, citric acid and monomethyl fumarate. The downstream metabolism of fumaric acid occurs through the tricarboxylic acid 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 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 monomethyl fumarate is short (approximately 1 hour) and no circulating monomethyl fumarate is present at 24 hours in the majority of individuals. Accumulation of parent drug or monomethyl fumarate 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 mg to 360 mg dose range studied.

#### Pharmacokinetics in special patient groups

Based on the results of Analysis of Variance (ANOVA), body weight is the main covariate of exposure (by  $C_{max}$  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 clinically significant impact on the pharmacokinetics of dimethyl fumarate. The pharmacokinetics in patients aged 65 and over has not been studied.

#### *Paediatric population*

The pharmacokinetic profile of 240 mg dimethyl fumarate twice a day was evaluated in a small, open-label, uncontrolled study in patients with RRMS aged 13 to 17 years (n=21). The pharmacokinetics of Tecfidera in these adolescent patients was consistent with that previously observed in adult patients ( $C_{max}$ :  $2.00 \pm 1.29$  mg/l;  $AUC_{0-12hr}$ :  $3.62 \pm 1.16$  h.mg/l, which corresponds to an overall daily AUC of 7.24 h.mg/l).

#### *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 dimethyl fumarate and monomethyl fumarate 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**

The adverse reactions described in the Toxicology and Reproduction toxicity sections below were not observed in clinical studies, but were seen in animals at exposure levels similar to clinical exposure levels.

#### Mutagenesis

Dimethyl fumarate and mono-methylfumarate were negative in a battery of *in vitro* assays (Ames, chromosomal aberration in mammalian cells). Dimethyl fumarate was negative in the *in vivo* micronucleus assay in the rat.

#### Carcinogenesis

Carcinogenicity studies of dimethyl fumarate were conducted for up to 2 years in mice and rats. Dimethyl fumarate was administered orally at doses of 25, 75, 200 and 400 mg/kg/day in mice, and at doses of 25, 50, 100, and 150 mg/kg/day in rats. In mice, the incidence of renal tubular carcinoma was increased at 75 mg/kg/day, at equivalent exposure (AUC) to the recommended human dose. In rats, the incidence of renal tubular carcinoma was increased at 100 mg/kg/day, approximately 2 times higher exposure than the recommended human dose. The relevance of these findings to human risk is unknown.

The incidence of squamous cell papilloma and carcinoma in the nonglandular stomach (forestomach) was increased at equivalent exposure to the recommended human dose in mice and below exposure to the recommended human dose in rats (based on AUC). The forestomach in rodents does not have a human counterpart.

#### Toxicology

Nonclinical studies in rodent, rabbits, and monkeys were conducted with a dimethyl fumarate suspension (dimethyl fumarate in 0.8% hydroxypropyl methylcellulose) administered by oral gavage. The chronic dog study was conducted with oral administration of the dimethyl fumarate capsule.

Kidney changes were observed after repeated oral administration of dimethyl fumarate in mice, rats, dogs, and monkeys. Renal tubule epithelial regeneration, suggestive of injury, was observed in all species. Renal tubular hyperplasia was observed in rats with life time dosing (2-year study). In dogs that received daily oral doses of dimethyl fumarate for 11 months, the margin calculated for cortical atrophy was observed at 3 times the recommended dose based on AUC. In monkeys that received daily oral doses of dimethyl fumarate for 12 months, single cell necrosis was observed at 2 times the recommended dose based on AUC. Interstitial fibrosis and cortical atrophy were observed at 6 times the recommended dose based on AUC. The relevance of these findings to humans is not known.

In the testes, degeneration of the seminiferous epithelium was seen in rats and dogs. The findings were observed at approximately the recommended dose in rats and 3 times the recommended dose in dogs (AUC basis). The relevance of these findings to humans is not known.

Findings in the forestomach of mice and rats consisted of squamous epithelial hyperplasia and hyperkeratosis; inflammation; and squamous cell papilloma and carcinoma in studies of 3 months or longer in duration. The forestomach of mice and rats does not have a human counterpart.

#### Reproduction toxicity

Oral administration of dimethyl fumarate to male rats at 75, 250, and 375 mg/kg/day prior to and during mating had no effects on male fertility up to the highest dose tested (at least 2 times the recommended dose on an AUC basis). Oral administration of dimethyl fumarate to female rats at 25, 100, and 250 mg/kg/day prior to and during mating, and continuing to Day 7 of gestation, induced reduction in the number of estrous stages per 14 days and increased the number of animals with prolonged diestrus at the highest dose tested (11 times the recommended dose on an AUC basis). However, these changes did not affect fertility or the number of viable fetuses produced.

Dimethyl fumarate has been shown to cross the placental membrane into fetal blood in rats and rabbits, with ratios of fetal to maternal plasma concentrations of 0.48 to 0.64 and 0.1 respectively. No malformations were observed at any dose of dimethyl fumarate in rats or rabbits. Administration of dimethyl fumarate at oral doses of 25, 100, and 250 mg/kg/day to pregnant rats during the period of organogenesis resulted in maternal adverse effects at 4 times the recommended dose on an AUC basis, and low fetal weight and delayed ossification (metatarsals and hindlimb phalanges) at 11 times the recommended dose on an AUC basis. The lower fetal weight and delayed ossification were considered secondary to maternal toxicity (reduced body weight and food consumption).

Oral administration of dimethyl fumarate at 25, 75, and 150 mg/kg/day to pregnant rabbits during organogenesis had no effect on embryo-fetal development and resulted in reduced maternal body weight at 7 times the recommended dose and increased abortion at 16 times the recommended dose, on an AUC basis.

Oral administration of dimethyl fumarate at 25, 100, and 250 mg/kg/day to rats during pregnancy and lactation resulted in lower body weights in the F1 offspring, and delays in sexual maturation in F1 males at 11 times the recommended dose on an AUC basis. There were no effects on fertility in the F1 offspring. The lower offspring body weight was considered secondary to maternal toxicity.



## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule contents (enteric-coated microtablets)

Microcrystalline cellulose  
Croscarmellose sodium  
Talc  
Silica, colloidal anhydrous  
Magnesium stearate  
Triethyl citrate  
Methacrylic acid – methyl methacrylate copolymer (1:1)  
Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%  
Simeticone  
Sodium laurilsulfate  
Polysorbate 80

#### Capsule shell

Gelatin  
Titanium dioxide (E171)  
Brilliant Blue FCF (E133)  
Yellow iron oxide (E172)

#### Capsule print (black ink)

Shellac  
Potassium hydroxide  
Black iron oxide (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

4 years

### **6.4 Special precautions for storage**

Do not store above 30°C.  
Keep the blisters in the outer carton in order to protect from light.

### **6.5 Nature and contents of container**

120 mg capsules: 14 capsules in PVC/PE/PVDC-PVC aluminium blister packs.  
240 mg capsules: 56 or 168 capsules in PVC/PE/PVDC-PVC aluminium blister packs.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

Biogen Netherlands B.V.  
Prins Mauritslaan 13  
1171 LP Badhoevedorp  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/13/837/001  
EU/1/13/837/002  
EU/1/13/837/003

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 30 January 2014  
Date of latest renewal: 20 September 2018

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Biogen (Denmark) Manufacturing ApS  
Biogen Allé 1  
DK-3400 Hillerød  
Denmark

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Tecfidera 120 mg gastro-resistant hard capsules  
dimethyl fumarate

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each gastro-resistant hard capsule contains 120 mg dimethyl fumarate

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 gastro-resistant hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use

Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C

Keep the blisters in the outer carton in order to protect from light

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Biogen Netherlands B.V.  
Prins Mauritslaan 13  
1171 LP Badhoevedorp  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/13/837/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Tecfidera 120 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC:  
SN:  
NN:



**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**HEAT SEALED BLISTER CARD**

**1. NAME OF THE MEDICINAL PRODUCT**

Tecfidera 120 mg gastro-resistant hard capsules  
dimethyl fumarate

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Biogen Netherlands B.V.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Morning  
Evening  
Mon.  
Tue.  
Wed.  
Thu.  
Fri.  
Sat.  
Sun.

*Sun as a symbol*  
*Moon as a symbol*

14 gastro-resistant hard capsules

**Oral use**

Each capsule contains 120 mg dimethyl fumarate

Read the package leaflet before use

Keep out of the sight and reach of children

**Do not store above 30°C**

**Keep the blisters in the outer carton in order to protect from light**

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Tecfidera 120 mg  
dimethyl fumarate

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Tecfidera 240 mg gastro-resistant hard capsules  
dimethyl fumarate

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each gastro-resistant hard capsule contains 240 mg dimethyl fumarate

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

56 gastro-resistant hard capsules  
168 gastro-resistant hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use

Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C  
Keep the blisters in the outer carton in order to protect from light

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Biogen Netherlands B.V.  
Prins Mauritslaan 13  
1171 LP Badhoevedorp  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/13/837/002  
EU/1/13/837/003

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Tecfidera 240 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**HEAT SEALED BLISTER CARD**

**1. NAME OF THE MEDICINAL PRODUCT**

Tecfidera 240 mg gastro-resistant hard capsules  
dimethyl fumarate

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Biogen Netherlands B.V.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Morning  
Evening  
Mon.  
Tue.  
Wed.  
Thu.  
Fri.  
Sat.  
Sun.

*Sun as a symbol*  
*Moon as a symbol*

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Tecfidera 240 mg  
dimethyl fumarate

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

**Tecfidera 120 mg gastro-resistant hard capsules**  
**Tecfidera 240 mg gastro-resistant hard capsules**  
dimethyl fumarate

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### What is in this leaflet

1. What Tecfidera is and what it is used for
2. What you need to know before you take Tecfidera
3. How to take Tecfidera
4. Possible side effects
5. How to store Tecfidera
6. Contents of the pack and other information

#### 1. What Tecfidera is and what it is used for

##### What Tecfidera is

Tecfidera is a medicine that contains the active substance **dimethyl fumarate**.

##### What Tecfidera is used for

**Tecfidera is used to treat relapsing-remitting multiple sclerosis (MS) in adult patients.**

MS is a long-term condition that affects the central nervous system (CNS), including the brain and the spinal cord. Relapsing-remitting MS is characterised by repeated attacks (relapses) of nervous system symptoms. Symptoms vary from patient to patient, but typically include walking difficulties, feeling off balance and visual difficulties (e.g. blurred or double vision). These symptoms may disappear completely when the relapse is over, but some problems may remain.

##### How Tecfidera works

Tecfidera seems to work by stopping the body's defence system from damaging your brain and spinal cord. This may also help to delay future worsening of your MS.

#### 2. What you need to know before you take Tecfidera

##### Do not take Tecfidera:

- **if you are allergic to dimethyl fumarate** or any of the other ingredients of this medicine (listed in section 6).



## Warnings and precautions

Tecfidera may affect your **white blood cell counts**, your **kidneys** and **liver**. Before you start Tecfidera, your doctor will do a blood test to count the number of your white blood cells and will check that your kidneys and liver are working properly. Your doctor will test these periodically during treatment. If your number of white blood cells decreases during treatment, your doctor may consider interrupting your treatment

**Talk to your doctor** before taking Tecfidera if you have:

- severe **kidney** disease
- severe **liver** disease
- a disease of the **stomach** or **bowel**
- a serious **infection** (such as pneumonia)

Herpes zoster (shingles) may occur with Tecfidera treatment. In some cases, serious complications have occurred. **You should inform your doctor** immediately if you suspect you have any symptoms of shingles.

A rare but serious kidney disorder (Fanconi Syndrome) has been reported for a medicine containing dimethyl fumarate, in combination with other fumaric acid esters, used to treat psoriasis (a skin disease). If you notice you are passing more urine, are more thirsty and drinking more than normal, your muscles seem weaker, you break a bone, or just have aches and pains, talk to your doctor as soon as possible so that this can be investigated further.

## Children and adolescents

Tecfidera is not recommended for use in children and adolescents because there is limited experience in the use of Tecfidera in this population.

## Other medicines and Tecfidera

**Tell your doctor or pharmacist** if you are taking, have recently taken or might take any medicines, in particular:

- medicines that contain **fumaric acid esters** (fumarates) used to treat psoriasis
- **medicines that affect the body's immune system** including **other medicines used to treat MS**, such as fingolimod, natalizumab, teriflunomide, alemtuzumab, ocrelizumab or cladribine, or some commonly used **cancer** treatments (rituximab or mitoxantrone).
- **medicines that affect the kidneys including** some **antibiotics** (used to treat infections), "**water tablets**" (*diuretics*), **certain types of painkillers** (such as ibuprofen and other similar anti-inflammatories and medicines purchased without a doctor's prescription) and medicines that contain **lithium**
- Taking Tecfidera with certain types of vaccines (*live vaccines*) may cause you to get an infection and should, therefore, be avoided. Your doctor will advise whether other types of vaccines (non-live vaccines) should be given.

## Tecfidera with alcohol

Consumption of more than a small quantity (more than 50 ml) of strong alcoholic drinks (more than 30% alcohol by volume, e.g. spirits) should be avoided within an hour of taking Tecfidera, as alcohol can interact with this medicine. This could cause inflammation of the stomach (*gastritis*), especially in people already prone to gastritis.

## Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

### Pregnancy

Do not use Tecfidera if you are pregnant unless you have discussed this with your doctor.

### Breast-feeding

It is not known whether the active substance of Tecfidera passes into breast milk. Tecfidera should not be used during breast-feeding. Your doctor will help you decide whether you should stop breast-feeding, or stop using Tecfidera. This involves balancing the benefit of breast-feeding for your child, and the benefit of therapy for you.

### **Driving and using machines**

The effect of Tecfidera on the ability to drive or use machines is not known. Tecfidera is not expected to affect your ability to drive and use machines.

## **3. How to take Tecfidera**

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

### **Starting dose**

#### **120 mg twice a day.**

Take this starting dose for the first 7 days, then take the regular dose.

### **Regular dose**

#### **240 mg twice a day.**

Tecfidera is for oral use

**Swallow each capsule whole**, with some water. Do not divide, crush, dissolve, suck or chew the capsule as this may increase some side effects.

**Take Tecfidera with food** – it may help to reduce some of the very common side effects (listed in section 4).

### **If you take more Tecfidera than you should**

If you have taken too many capsules, **talk to your doctor straight away**. You may experience side effects similar to those described below in section 4.

### **If you forget to take Tecfidera**

If you forget or miss a dose, **do not take a double dose**.

You may take the missed dose if you leave at least 4 hours between the doses. Otherwise wait until your next planned dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

## Serious effects

Moderately low to very low lymphocyte counts - Lymphocyte counts (a type of white blood cell) may be decreased for a long period of time. Having a low white blood cell count for a long period of time can increase your risk of infection, including a risk of a rare brain infection called progressive multifocal leukoencephalopathy (PML). The symptoms of PML may be similar to an MS relapse. Symptoms may include new or worsening weakness on one side of the body; clumsiness; changes in vision, thinking, or memory; or confusion or personality changes lasting for more than several days.

→ **Call your doctor straight away if you experience any of these symptoms**

## Severe Allergic reactions

The frequency of severe allergic reactions cannot be estimated from the available data (not known).

Reddening of the face or body (*flushing*) is a very common side effect. However, should flushing be accompanied by a red rash or hives **and** you get any of these symptoms:

- swelling of the face, lips, mouth or tongue (*angioedema*)
- wheezing, difficulty breathing or shortness of breath (*dyspnoea, hypoxia*)
- dizziness or loss of consciousness (*hypotension*)

then this may represent a severe allergic reaction (*anaphylaxis*)

→ **Stop taking Tecfidera and call a doctor straight away**

## Very common side effects

These may affect *more than 1 in 10 people*:

- reddening of the face or body feeling warm, hot, burning or itchy (*flushing*)
- loose stools (*diarrhoea*)
- feeling sick (*nausea*)
- stomach pain or stomach cramps

→ **Taking your medicine with food** can help to reduce the side effects above

Substances called ketones, which are naturally produced in the body, very commonly show up in urine tests while taking Tecfidera.

**Talk to your doctor** about how to manage these side effects. Your doctor may reduce your dose. Do not reduce your dose unless your doctor tells you to.

## Common side effects

These may affect *up to 1 in 10 people*:

- inflammation of the lining of the intestines (*gastroenteritis*)
- being sick (*vomiting*)
- indigestion (*dyspepsia*)
- inflammation of the lining of the stomach (*gastritis*)
- gastrointestinal disorder
- burning sensation
- hot flush, feeling hot
- itchy skin (*pruritus*)
- rash
- pink or red blotches on the skin (*erythema*)

Side effects which may show up in your blood or urine tests

- low levels of white blood cells (*lymphopenia, leucopenia*) in the blood. Reduced white blood cells could mean your body is less able to fight an infection. If you have a serious infection (such as pneumonia), talk to your doctor immediately
- proteins (*albumin*) in urine
- increase in levels of liver enzymes (*ALT, AST*) in the blood

### Uncommon side effects

These may affect *up to 1 in 100 people*:

- Allergic reactions (*hypersensitivity*)
- reduction in blood platelets

**Not known** (frequency cannot be estimated from the available data)

- liver inflammation and increase in levels of liver enzymes (*ALT or AST in combination with bilirubin*)

- herpes zoster (shingles) with symptoms such as blisters, burning, itching or pain of the skin, typically on one side of the upper body or the face, and other symptoms, like fever and weakness in the early stages of infection, followed by numbness, itching or red patches with severe pain

### Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Tecfidera

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after “EXP”. The expiry date refers to the last day of that month.

Do not store above 30°C.

Keep the blisters in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Tecfidera contains

**The active substance** is dimethyl fumarate.

Tecfidera 120 mg: Each capsule contains 120 mg of dimethyl fumarate.

Tecfidera 240 mg: Each capsule contains 240 mg of dimethyl fumarate.

**The other ingredients** are microcrystalline cellulose, croscarmellose sodium, talc, silica colloidal anhydrous, magnesium stearate, triethyl citrate, methacrylic acid – methyl methacrylate copolymer (1:1), methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%, simeticone, sodium laurilsulfate, polysorbate 80, gelatin, titanium dioxide (E171), brilliant blue FCF (E133), yellow iron oxide (E172), shellac, potassium hydroxide and black iron oxide (E172).

### What Tecfidera looks like and contents of the pack

Tecfidera 120 mg gastro-resistant hard capsules are green and white and printed with 'BG-12 120 mg' and are available in packs containing 14 capsules.

Tecfidera 240 mg gastro-resistant hard capsules are green and printed with 'BG-12 240 mg' and are available in packs containing 56 or 168 capsules.

Not all pack sizes may be marketed.

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**This leaflet was last revised in {MM YYYY}.**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

**Annex IV**

**Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)**

### **Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for dimethyl fumarate (multiple sclerosis), the scientific conclusions of CHMP are as follows:

There was no case explicitly reporting Fanconi syndrome in the Multiple Sclerosis (MS) indication; however, it has been reported in literature that female patients with psoriasis treated long-term with fumaric acid esters seem to be at particular risk. The limited long-term experience with Tecfidera could contribute to the low evidence regarding a potential association of dimethyl fumarate and Fanconi syndrome in the MS indication. Since early diagnosis of Fanconi syndrome and discontinuation of the potentially causative drug, e.g. dimethyl fumarate, are important steps to prevent the onset of renal impairment and osteomalacia, the PRAC recommends the inclusion of a warning in SmPC section 4.4 to make physicians aware of the potential risk of Fanconi syndrome including the description of corresponding symptoms. The Package leaflet should be updated accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

### **Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for dimethyl fumarate (multiple sclerosis) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing dimethyl fumarate (multiple sclerosis) is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.