

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 capsule

Each capsule contains 120 mg dimethyl fumarate. Tecfidera 240mg

capsule

Each 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).

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.
Suspected or confirmed Progressive Multifocal Leukoencephalopathy (PML)

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 (≥ 3 upper limit of normal (ULN)) and elevation of total bilirubin levels (≥ 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 lymphopenia (see section 4.8).

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.

Dimethyl fumarate has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients..

Tecfidera should not be initiated in patients with severe lymphopenia (lymphocyte counts $<0.5 \times 10^9/L$).

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

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

- Tecfidera should be discontinued in patients with prolonged severe lymphopenia (lymphocyte counts $<0.5 \times 10^9/L$) persisting for more than 6 months.
- In patients with sustained moderate reductions of absolute lymphocyte counts $\geq 0.5 \times 10^9/L$ and $<0.8 \times 10^9/L$ for more than six months the benefit / risk of Tecfidera treatment should be re-assessed.
- In patients with lymphocyte counts below lower limit of normal (LLN) as defined by local laboratory reference range, regular monitoring of absolute lymphocyte counts is recommended. Additional factors that might further augment the individual PML risk should be considered (see subsection on PML below).

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.

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 has been reported in patients treated with Tecfidera (see section 4.8).. PML is an opportunistic infection caused by John-Cunningham virus (JCV), which may be fatal or result in severe disability.

PML cases have occurred with dimethyl fumarate and other medicinal products containing fumarates in the setting of lymphopenia (lymphocyte counts below LLN). Prolonged moderate to severe lymphopenia appears to increase the risk of PML with Tecfidera, however, risk cannot be excluded in patients with mild lymphopenia.

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

- duration of Tecfidera therapy. Cases of PML have occurred after approximately 1 to 5 years of treatment, although the exact relationship with duration of treatment is unknown.
- profound decreases in CD4+ and especially in CD8+ T cell counts, which are important for immunological defence (see section 4.8), and

- prior immunosuppressive or immunomodulatory therapy (see below).

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

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

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

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 possible.

PML cases have occurred in patients who had previously been treated with natalizumab, for which PML is an established risk. Physicians should be aware that cases of PML occurring following recent discontinuation of natalizumab may not have lymphopenia.

In addition, a majority of confirmed PML cases with Tecfidera occurred in patients with prior immunomodulatory treatment.

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).

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 ≥ 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 ≥ 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)	Not known
	Herpes Zoster ¹	Not known
Blood and lymphatic system disorders	Lymphopenia	Common
	Leucopenia	Common
	Thrombocytopenia	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylaxis ¹	Not known
	Dyspnoea ¹	Not known
	Hypoxia ¹	Not known

	Hypotension ¹	Not known
	Angioedema ¹	Not known
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 ¹	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

¹ 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 ≥ 3 times ULN, respectively, were seen in 5% and 2% of patients treated with placebo and 6% and 2% of patients treated with Tecfidera. Discontinuations due to elevated hepatic transaminases were <1% and similar in patients treated with Tecfidera or placebo. Elevations in transaminases ≥ 3 times ULN with concomitant elevations in total bilirubin >2 times ULN, were not observed in placebo-controlled studies.

Increase of liver enzymes and cases of drug-induced liver injury (elevations in transaminases ≥ 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.

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), 41% of patients treated with Tecfidera had lymphopenia (defined in these studies as $<0.91 \times 10^9/L$). Mild lymphopenia (counts $\geq 0.8 \times 10^9/L$ and $<0.91 \times 10^9/L$) was observed in 28% of patients; moderate lymphopenia (counts $\geq 0.5 \times 10^9/L$ and $<0.8 \times 10^9/L$) persisting for at least six months was observed in 10% of patients; severe lymphopenia (counts $<0.5 \times 10^9/L$) persisting for at least six months was observed in 2% of patients. In the group with severe lymphopenia, the majority of lymphocyte counts remained $<0.5 \times 10^9/L$ with continued therapy.

In addition, in an uncontrolled, prospective, post-marketing study, at week 48 of treatment with Tecfidera (n=185) CD4+ T cells were moderately (counts $\geq 0.2 \times 10^9/L$ to $<0.4 \times 10^9/L$) or severely ($<0.2 \times 10^9/L$) decreased in up to 37 % or 6 % of patients, respectively, while CD8+ T cells were more frequently reduced with up to 59 % of patients at counts $<0.2 \times 10^9/L$ and 25 % of patients at counts $<0.1 \times 10^9/L$.

Infections, including PML and opportunistic infections

Cases of infections with John Cunningham virus (JCV) causing Progressive Multifocal Leukoencephalopathy (PML) have been reported with Tecfidera (see section 4.4). PML may be fatal or result in severe disability. In one of the clinical trials, one patient taking Tecfidera developed PML in the setting of prolonged severe lymphopenia (lymphocyte counts predominantly $<0.5 \times 10^9/L$ for 3.5 years), with a fatal outcome. In the post-marketing setting, PML has also occurred in the presence of moderate and mild lymphopenia ($>0.5 \times 10^9/L$ to $<LLN$, as defined by local laboratory reference range).

In several PML cases with determination of T cell subsets at the time of diagnosis of PML, CD8+ T cell counts were found to be decreased to $<0.1 \times 10^9/L$, whereas reductions in CD4+ T cells counts were

variable (ranging from <0.05 to $0.5 \times 10^9/L$) and correlated more with the overall severity of lymphopenia ($<0.5 \times 10^9/L$ to $<LLN$). Consequently, the CD4+/CD8+ ratio was increased in these patients.

Prolonged moderate to severe lymphopenia appears to increase the risk of PML with Tecfidera, however, PML also occurred in patients with mild lymphopenia. Additionally, the majority of PML cases in the post-marketing setting have occurred in patients >50 years.

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. In a majority of subjects with concurrent lymphocyte counts below the LLN, lymphopenia was rated moderate or severe. 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 moderate ($<0.8 \times 10^9/L$ to $0.5 \times 10^9/L$) or severe ($<0.5 \times 10^9/L$ to $0.2 \times 10^9/L$) 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

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_H1, T_H17), and biased towards anti-inflammatory production (T_H2). 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
Clinical Endpoints^a					
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#	0.156#
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)
MRI Endpoints^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)

^aAll analyses of clinical endpoints were intent-to-treat; ^bMRI 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 CO₂ 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±1.29 mg/l; AUC_{0-12hr}: 3.62±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

Tecfidera 120mg	Tecfidera 240mg
<p><u>Microtablets:</u> <u>Core-</u> Microcrystalline cellulose Dimethyl fumarate Talc Croscarmellose sodium</p> <p>Magnesium stearate Silica, colloidal anhydrous</p> <p><u>Seal coating-</u> Methacrylic acid– methyl methacrylate copolymer 1:1 Triethyl citrate Sodium laurel sulfate</p> <p><u>Enteric coating-</u> Methacrylic acid–ethyl acrylate copolymer (1:1) dispersion 30% Talc, micronized Triethyl citrate Polysorbate 80 Sodium laurilsulfate</p> <p>Simeticone</p> <p><u>Gelatin capsule:</u> <u>Body-</u> Gelatin Titanium dioxide Black ink <u>Cap-</u> Gelatin Titanium dioxide Yellow iron oxide Brilliant blue FCF – FD&C blue 1 blue 1 Black ink</p>	<p><u>Microtablets:</u> <u>Core-</u> Dimethyl fumarate Microcrystalline cellulose Silica, colloidal anhydrous Croscarmellose sodium</p> <p>Magnesium stearate</p> <p><u>Seal coating-</u> Methacrylic acid methyl methacrylate copolymer 1:1 Triethyl citrate Sodium laurel sulfate</p> <p><u>Enteric coating-</u> Methacrylic acid–ethyl acrylate copolymer (1:1) dispersion 30% Talc, micronized Triethyl citrate Polysorbate 80 Sodium laurilsulfate</p> <p>Simeticone</p> <p><u>Gelatin capsule:</u> <u>Body-</u> Gelatin Titanium dioxide Yellow iron oxide Brilliant blue FCF – FD&C blue 1 Black ink <u>Cap-</u> Gelatin Titanium dioxide Yellow iron oxide Brilliant blue FCF – FD&C blue 1 Black ink</p>

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging material.

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 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 Idec Ltd
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

8. LICENSE HOLDER

Medison Pharma Ltd., POB 7090, Petach Tikva

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