Physician Prescribing Information

NAME OF THE MEDICINAL PRODUCT

Vumerity 231 mg
diroximel fumarate 231 mg
Delayed-release capsule

Pharmaceutical form

Gastro-resistant hard capsules
White capsules with gastro-resistant microtablets containing 231 mg of the active substance diroximel fumarate and printed with “DRF 231 mg”.

Therapeutic Indications

VUMERITY is indicated for the treatment of adult patients with relapsing remittind forms of multiple sclerosis.

Dosage/Administration

General information

Treatment with Vumerity must be started and monitored by a neurologist experienced in treating MS patients.
Treatment with Vumerity can be started on the day after treatment with dimethyl fumarate has been stopped.

Method of administration

Vumerity is for oral use.
Vumerity should be swallowed whole and intact. Vumerity should not be crushed, divided, sprinkled, sucked, or chewed.
VUMERITY may be taken with or without food. Administration of VUMERITY with food may reduce the incidence of flushing. If taken with food, avoid a high-calorie meal/snack; the meal/snack should contain no more than 700 calories and no more than 30 g fat.

Dosage

Adults

The starting dose for Vumerity is 231 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 462 mg (administered as two 231 mg capsules) twice a day orally.
Temporary dose reductions to 231 mg twice a day may be considered for patients who do not tolerate the maintenance dose due to adverse effects. Within 4 weeks, the recommended dose (462 mg twice a day) should be resumed. Discontinuation of Vumerity should be considered for patients unable to tolerate resumption of the maintenance dose.

Administration of non-gastro-resistant acetylsalicylic acid 30 minutes prior to Vumerity dosing may reduce the occurrence and severity of flushing (See “Undesirable effects”).
Avoid co-administration of Vumerity with alcohol (see “Pharmacokinetics”).

Special patient groups

Elderly

The efficacy and safety of Vumerity have not been investigated in patients over 55 years of age.

Children and adolescents

The safety and efficacy of in children and adolescents under the age of 18 years have not yet been established.

Patients with renal or hepatic impairment

A single-dose clinical study of Vumerity was conducted in patients with mild, moderate, and severe renal impairment. The degree of renal impairment had no effect on exposure to the active primary metabolite monomethyl fumarate (MMF). The long-term safety of Vumerity in patients with moderate or severe renal impairment has not been investigated.
Vumerity has not been studied in patients with hepatic impairment.
Treatment of patients with moderate and severe kidney function disorder or mild, moderate and severe liver function disorders is contraindicated (see “Contraindications”).

Contraindications

Hypersensitivity to diroximel fumarate, dimethyl fumarate or to any of the excipients.
Moderately or severely impaired kidney function and mildly, moderately or severely impaired liver function (using Child-Pugh score).
Infection with the human immunodeficiency virus (HIV).
Serious active infections, active chronic infections (e.g. tuberculosis, hepatitis B and C).
Severe gastrointestinal disorders such as gastric ulcers and duodenal ulcers.
Leukopenia under $<3.0 \times 10^9$/L.
Lymphopenia under $< 0.5 \times 10^9$/L.
Progressive multifocal leukoencephalphathy (PML) or suspicion of PML.
Children and adolescents under 18 years of age.
Start of treatment during pregnancy.

Warnings and precautions

General information

Vumerity and dimethyl fumarate are metabolized to monomethyl fumarate after oral administration (See “Pharmacokinetics”). The risks associated with Vumerity are expected to be similar to those reported for dimethyl fumarate, even though not all the risks listed below have been observed specifically with Vumerity.
During treatment with Vumerity, simultaneous use of other (topical or systemic) fumaric acid derivatives must be avoided.

Anaphylaxis and angioedema

Cases of anaphylaxis have been reported during treatment with dimethyl fumarate (which has the same active metabolite as Vumerity). These reactions generally occurred after the first dose, but may occur at any timepoint during treatment, and may be serious and life-threatening. Patients must be informed about the potential symptoms of anaphylaxis such as difficulty breathing, urticaria or swelling of the throat/tongue and be advised to suspend treatment in such cases and to seek medical assistance immediately. Treatment should not be restarted.

Haematology

Prior to initiating treatment with Vumerity, a current complete blood count, including lymphocytes, must be performed. If the lymphocyte count is below the lower limit of normal, a comprehensive investigation of possible causes should be carried out before initiating therapy

with Vumerity. Vumerity may decrease lymphocyte counts (see “Undesirable effects”). In placebo-controlled studies performed with MS patients, the lymphocyte count dropped by about 30% during the first year of treatment with dimethyl fumarate and remained stable afterwards. A reduced lymphocyte count of $<0.5 \times 10^9$/L and a reduced leukocyte count of $<3.0 \times 10^9$/L was observed in 6%-7% of patients treated with dimethyl fumarate. In clinical studies, 2% of patients experienced lymphocyte counts $<0.5 \times 10^9$/L for at least 6 months. In these patients, the majority of lymphocyte counts remained $<0.5 \times 10^9$/L with continued therapy. Accordingly, patients with lymphocyte counts $<0.5 \times 10^9$/L for at least 6 months appear to have an increased risk of severe and prolonged lymphopenia.

In a pooled subgroup analysis of controlled and uncontrolled clinical studies, the mean overall time for lymphocyte counts to return to normal after discontinuing dimethyl fumarate treatment is estimated to be 4.7 weeks (95 % CI: 0, 16.2) in patients without prolonged, severe lymphopenia and 29 weeks (95% CI: 0, 61.1) in patients with prolonged (for six months or longer), severe ($<0.5 \times 10^9$/L) lymphopenia (2% of the total population) (see “Undesirable effects”).

In EVOLVE-MS-1, a 96-week, open label clinical study, Vumerity was discontinued in patients with confirmed lymphocyte counts $<0.5 \times 10^9$/L which persisted for ≥4 weeks. In an interim analysis of this study, 12.3% of patients (n = 129) had lymphocyte counts $\geq 0.5 \times 10^9$/L and $<0.8 \times 10^9$/L for at least 6 months, 1.5% (n = 16) of patients discontinued Vumerity due to confirmed lymphocyte counts $<0.5 \times 10^9$/L which persisted for ≥4 weeks, and an additional 0.5% (n = 5) of patients who discontinued treatment with Vumerity due to low lymphocyte or leukocyte counts had at least one lymphocyte value of $<0.5 \times 10^9$/L.

Vumerity has not been studied in patients with pre-existing low lymphocyte or leukocyte counts or in patients undergoing simultaneous immunomodulating treatments, so caution should be exercised when treating these patients.

Therapy must not be started if there is lymphopenia $<0.5 \times 10^9$/L or leukopenia $<3.0 \times 10^9$/L. Prior to initiating treatment with Vumerity, a recent full blood count that includes a differential blood count must be available. A close analysis of the full blood counts is recommended at least every 3 months in the first 1.5 years of treatment and at least every 6 to 12 months thereafter and as clinically indicated. 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 (persistent moderate lymphopenia).

If therapy is continued in the presence of moderate to severe prolonged lymphopenia, the risk of an opportunistic infection, including progressive multifocal leukoencephalopathy (PML) cannot be ruled out. At the first signs or symptoms suggestive of PML, withhold Vumerity and perform appropriate diagnostic evaluations. The benefit/risk should be assessed in patients with lymphocyte counts ≥0.5 × 10^9/L und <0.8 × 10^9/L for more than 6 months.

If the leukocyte count drops considerably – particularly to levels of <3.0 × 10^9/L – and the lymphocyte count drops to <0.5 × 10^9/L, then therapy with Vumerity should be interrupted. Alternative causes of lymphopenia must be ruled out. In case of severe and prolonged lymphopenia there is a risk of an opportunistic infection (such as progressive multifocal leukoencephalopathy, PML) and in such a case the therapy must be discontinued (see “Contraindications”).

If blood parameters do not return to normal levels within one month and therapy with Vumerity cannot be started again, or if a significant drop in the number of leukocytes or lymphocytes occurs during the further course of therapy, then switching to an alternative therapy must be considered.

A full blood count is also recommended before switching to a different therapy if it is also known to potentially cause a reduction in the lymphocyte count.

Active infections

Therapy with Vumerity must not be started in patients with signs or symptoms of a serious active infection.
Owing to the potential risk of infection under persistent lymphopenia, patients must be instructed to report symptoms of an infection to the treating physician. In cases of a serious infection during treatment with Vumerity, interrupting the therapy must be considered until the infection has receded.

Opportunistic infections / progressive multifocal leukoencephalopathy (PML)

Cases of PML have occurred in patients with lymphopenia (< 0.91 × 10^9/L) being treated with dimethyl fumarate (which has the same active metabolite as Vumerity) and other fumarate-containing medications. The role of the lymphopenia in these cases is unknown, however these

PML cases have occurred predominantly in the connection with prolonged moderate to severe lymphopenia (<0.8x10^9/L over >6 months).
PML is an opportunistic viral infection of the brain caused by John Cunningham virus (JCV) that may lead to death or severe disability. The symptoms of PML may be similar to a MS relapse. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. At the first sign or symptom suggestive of PML, withhold Vumerity and perform an appropriate diagnostic evaluation.

Additionally, PML cases have occurred in patients who had been treated previously with natalizumab (Natalizumab is associated with an increased risk for developing PML). Therefore, if switching from disease modifying therapies and/or immunosuppressants to Vumerity caution is advised and at least in the first treatment months close clinical progress assessments should take place.

Serum anti-JCV antibody testing is not validated as a risk assessment tool for PML in Vumerity-treated patients. If anti-JCV antibody testing is undertaken, it should be considered that the influence of lymphopenia on the accuracy of the anti-JCV antibody test has not been studied in Vumerity-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.
Patients should be encouraged by their treating physician to inform people they trust or care for about their treatment as they may perceive symptoms that are not noticed by the patient.

Vaccination

The safety of immunisation with live viral vaccines during treatment with Vumerity has not been investigated in clinical trials. Live vaccines have the potential risk of causing a clinical infection and are not recommended during treatment with Vumerity.

Liver and kidney function

Changes in renal and hepatic laboratory values have been seen in clinical trials in subjects treated with dimethyl fumarate (see “Undesirable effects”). The clinical implications of these changes are unknown.

Kidney function

Assessments of renal function (serum creatinine, blood urea nitrogen concentration and urinalysis, including protein and urine sediment) are recommended prior to treatment initiation, after 6 months of treatment and every 6 to 12 months thereafter and as clinically indicated.

Patients with moderate or severe renal impairment must not be treated (see "Contraindications").

Vumerity should be used with caution in patients with mild renal impairment.

Treatment with Vumerity of patients who are under long-term therapy with drugs that pose a potential nephrotoxic risk (e.g. aminoglycosides, diuretics, non-steroidal anti-inflammatory drugs, lithium) has not been investigated, so such patients should only be treated with caution.

Liver function

Drug-induced liver injury, including liver enzyme increase (≥3 ULN) and elevation of total bilirubin levels (≥2 ULN) can result from treatment with Vumerity. Liver damage can occur immediately, or after several weeks or longer, and may require hospitalization. Resolution of the adverse events was observed after treatment was discontinued.
Assessment of liver function (ALT, AST, gamma-GT, alkaline phosphatase and serum bilirubin) is recommended prior to treatment initiation, after 6 months of treatment and every 6 to 12 months thereafter and as clinically indicated.
Patients with hepatic impairment of any degree of severity must not be treated (see "Contraindications").

Vascular disorders (flushing)

Vumerity can cause flush symptoms (e.g. reddening, rashes, hot flushes, itching and/or burning paraesthesia).

In placebo-controlled studies performed on patients with multiple sclerosis treated with dimethyl fumarate, 34% had flushing, compared with 5% on placebo. Flushing symptoms began soon after treatment with dimethyl fumarate was started and improved or stopped during the further course of therapy.
Taking Vumerity with food may reduce the incidence of flushing (see "Dosage/Administration").

Administration of non-gastro-resistant acetylicsalicylic acid prior to Vumerity dosing may reduce the occurrence and severity of flushing (see “Interactions”). Temporary dose reductions to 231 mg twice a day may be considered for patients who do not tolerate the maintenance dose. However, taking acetylsalicylic acid over a longer period of time is not recommended (see also “Dosage/Administration”, “Interactions”, “Undesirable effects” and “Pharmacokinetics”).

Carcinogenicity

Higher incidences of Leydig cell adenomas were observed in male rat testicles treated with diroximel fumarate (see section “Preclinical data”). The significance of this finding for the risk to humans is unknown.

Herpes Zoster Infections

Serious cases of herpes zoster have occurred with dimethyl fumarate (which has the same active metabolite as Vumerity), including disseminated herpes zoster, herpes zoster ophthalmicus, herpes zoster meningoencephalitis and herpes zoster meningomyelitis. These events may occur at any time during treatment. Monitor patients on Vumerity for signs and symptoms of herpes zoster. If herpes zoster occurs, appropriate treatment for herpes zoster should be administered. Consider withholding Vumerity treatment in patients with serious infections until the infection has resolved (see “Undesirable effects/Post-Marketing Experience”).

Interactions

Vumerity has not been studied in combination with anti-neoplastic or immunosuppressive therapies. The concomitant use of these substances with Vumerity can increase the risk of infections, including opportunistic infections, and must therefore be avoided. Patients who have already been treated with immunosuppressants are at greater risk of developing infections. In these patients, it must be ensured that immunocompetence is sufficiently restored. 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 the infection rate.

The safety and efficacy of Vumerity in combination with immunomodulating therapies (beta interferons, glatiramer acetate) have not yet been conclusively researched in clinical studies and have been insufficiently investigated in pharmacokinetic studies. Therefore, caution must be exercised when using such combinations.

Diroximel fumarate metabolism does not involve CYP enzymes, so no clinically meaningful interactions are expected when it is administered with CYP inhibitors or inducers.
In vitro studies found that diroximel fumarate and its metabolites did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 enzymes in human liver microsomes or induce CYP1A2, CYP2B6, or CYP3A4/5 in cultured human hepatocytes.
A clinical pharmacokinetic (PK) study with digoxin and Vumerity showed that diroximel fumarate did not inhibit P-gp in vivo. The circulating inactive major metabolite of diroximel fumarate, HES, did not inhibit P-gp and was neither a substrate nor an inhibitor of BCRP, MATE1, MATE2-K, OAT1, OAT3, or OCT2.
Acetylsalicylic acid, when administered approximately 30 minutes before dimethyl fumarate, did not alter the pharmacokinetics of MMF.

A pharmacokinetic study with a combined oral contraceptive and dimethyl fumarate was conducted. There were no relevant effects of dimethyl fumarate on the pharmacokinetic profile of norelgestromin and ethinyl estradiol. No interaction studies have been performed with oral contraceptives containing other progestogens; however an effect of Vumerity on their exposure is not expected.

Medicinal products used in patients with multiple sclerosis, interferon beta-1a administered intramuscularly and glatiramer acetate administered subcutaneously, were tested for potential interactions with dimethyl fumarate in healthy subjects in two pharmacokinetic interaction studies and did not formally alter the pharmacokinetic profile of dimethyl fumarate. However, in these interaction studies, only single doses of the interacting substances were administered and the study was too short to assess pharmacodynamic interactions or a lower tolerability under joint administration.

Administration of 325 mg (or equivalent) non-gastro-resistant acetylsalicylic acid, 30 minutes prior to dimethyl fumarate over 4 days dosing, did not alter the pharmacokinetic profile of monomethyl fumarate and reduced the occurrence and severity of flushing in a study of healthy volunteers.

Patients treated with dimethyl fumarate were able to mount an effective immune response to inactivated neoantigen (first vaccination, conjugated meningococcal C polysaccharide vaccine),

recall antigen (re-exposure to the tetanus-diphtheria vaccine), or polysaccharide antigen (pneumococcal vaccine) in a clinical study in patients with relapsing forms of MS.

However, smaller increases in antibodies were documented for the tetanus and pneumococcal vaccinations in the dimethyl fumarate group than in the comparator group of patients undergoing treatment with non-pegylated interferons. Patients taking dimethyl fumarate may receive non-live vaccines. If possible it is recommended to administer routine vaccinations with non-live vaccines before treatment initiation with dimethyl fumarate.

No clinical data are available on the efficacy and safety of live attenuated vaccines in patients taking Vumerity. Live vaccines are not recommended during treatment with Vumerity due to the potential risk of a clinical infection.

Concurrent therapy with nephrotoxic medicinal products may increase the potential of renal adverse reactions (e.g. proteinuria) in patients taking Vumerity (see “Undesirable effects”, “Warnings and Precautions”).

Children and adolescents

Interaction studies have only been performed in adults.

Pregnancy, lactation

Pregnancy

There are no adequate and well-controlled data regarding the use of Vumerity by pregnant women. Animal studies have shown reproductive toxicity (see “Preclinical data”).The start of treatment during pregnancy is contraindicated (see section “Contraindications”). Women of childbearing potential must use suitable contraception measures. Vumerity is not recommended during pregnancy. If a woman being treated with Vumerity becomes pregnant, discontinuation of the therapy must be considered. Vumerity should be used during pregnancy only if the clinical finding for the patient provides a compelling reason for treatment and if the potential benefit justifies the potential risk to the foetus.

Lactation

It is unknown whether diroximel fumarate or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made on an individual basis on

whether to discontinue breast-feeding or to discontinue Vumerity therapy. The benefit of breast-feeding for the child and the benefit of therapy for the woman should be taken into account.

Effects on ability to drive and use machines

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

Undesirable effects

After oral administration, Vumerity and dimethyl fumarate are rapidly metabolized to monomethyl fumarate before they reach the systemic circulation. Adverse reactions are for Vumerity are expected to be similar to those of dimethyl fumarate after they have been metabolized.
The most common adverse drug reactions (incidence ≥10%) for patients treated with dimethyl fumarate were flushing and gastrointestinal events (i.e. diarrhea, nausea, abdominal pain, abdominal pain upper). The most commonly reported adverse reactions leading to discontinuation (incidence >1%) in patients treated with dimethyl fumarate were flushing (3%) and gastrointestinal events (4%). It has been demonstrated that Vumerity has fewer serious GI adverse events than dimethyl fumarate.

There are two phase 3 clinical trials with Vumerity in patients with relapsing-remitting MS (RRMS): EVOLVE-MS-1, an ongoing, open-label, 2-year safety study; and EVOLVE-MS-2, a completed, randomized, double-blind study comparing the GI tolerability of Vumerity to dimethyl fumarate. In these studies, the adverse reaction profile observed with Vumerity was similar to that seen with dimethyl fumarate in clinical trials.

In placebo-controlled and uncontrolled clinical studies, a total of 2513 patients have received dimethyl fumarate and have been followed for periods up to 12 years with an overall exposure equivalent to 11,318 person-years. A total of 1’169 patients have received at least 5 years of treatment with dimethyl fumarate, and 426 patients have received at least ten years of treatment with dimethyl fumarate. The experience in uncontrolled clinical trials is consistent with the experience in the placebo-controlled clinical trials.

The adverse reactions more frequently reported in patients taking dimethyl fumarate versus placebo-treated patients are presented below. These data are from two Phase 3 placebo-controlled, double-blind clinical trials with a total of 1’529 patients treated with dimethyl fumarate

and for up to 24 months with an overall exposure of 2’371 person-years (see section “Properties/Effects”). The frequencies given below are based on studies performed on 769 patients treated with dimethyl fumarate 240 mg twice a day and 771 patients treated with placebo.

The adverse reactions are presented using the corresponding MedDRA terms under each MedDRA System Organ Class. The incidence of the adverse reactions below is expressed according to the following categories:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Infections and infestations

Common: Gastroenteritis.

Blood and lymphatic system disorders

Common: Lymphopenia, leukopenia.

Immune system disorders

Uncommon: Hypersensitivity.

Nervous system disorders

Common: Burning sensation.

Vascular disorders

Very common Flushing (35%, placebo: 4%).
Common: Hot flush.

Gastrointestinal disorders

Very common: Diarrhea (14%, placebo: 11%), nausea (12%, placebo: 9%), abdominal pain upper (10%, placebo: 6%), abdominal pain (10%, placebo: 5%).
Common: Vomiting, dyspepsia, gastritis, gastrointestinal disorder.

Hepatobiliary disorders

Common: Aspartate aminotransferase increased, alanine aminotransferase increased.

Skin and subcutaneous tissue disorders

Common: Pruritus, rash, erythema.

Renal and urinary disorders

Common: Proteinuria.

General disorders and administration site conditions

Common: Feeling hot.

Investigations

Very common: Urine ketone bodies present (63%, placebo: 26%).
Common: Albumin urine, white blood cell count decreased.

Table 1 lists the adverse effects requiring treatment which occurred in ≥1% of patients treated with dimethyl fumarate with an incidence that was at least ≥1% higher than for those patients taking placebo in the two phase 3 placebo-controlled studies.

Adverse Event	*Placebo* *n = 771*	*Dimethyl Fumarate 240 mg twice daily* *n = 769*
Flushing	33 (4.3%)	265 (34.5%)
Nasopharyngitis	159 (20.6%)	170 (22.1%)
Diarrhea	83 (10.8%)	107 (13.9%)
Urinary Tract Infection	95 (12.3%)	107 (13.9%)
Upper Respiratory Tract Infection	87 (11.3%)	99 (12.9%)
Nausea	67 (8.7%)	93 (12.1%)
Abdominal Pain Upper	45 (5.8%)	76 (9.9%)
Abdominal Pain	37 (4.8%)	73 (9.5%)
Proteinuria	59 (7.7%)	67 (8.7%)
Vomiting	37 (4.8%)	65 (8.5%)
Pruritus	30 (3.9%)	62 (8.1%)
Rash	26 (3.4%)	58 (7.5%)
Hot Flush	16 (2.1%)	52 (6.8%)
Albumin Urine Present	27 (3.5%)	46 (6.0%)
Alanine Aminotransferase Increased	38 (4.9%)	45 (5.9%)

Gastroenteritis	28 (3.6%)	42 (5.5%)
Erythema	10 (1.3 %)	36 (4.7%)
Dyspepsia	20 (2.6%)	35 (4.6%)
Microalbuminuria	24 (3.1%)	35 (4.6%)
Aspartate Aminotransferase Increased	18 (2.3%)	33 (4.3%)
Gastritis	11 (1.4%)	22 (2.9%)
Burning Sensation	13 (1.7%)	21 (2.7%)
Abdominal Discomfort	11 (1.4%)	19 (2.5 %)
Gastrointestinal Disorder	8 (1.0%)	18 (2.3%)
Lymphopenia	2 (0.3%)	18 (2.3%)
Blood Urine Present	7 (0.9%)	16 (2.1%)
Dry Mouth	6 (0.8%)	16 (2.1%)
Blood Parathyroid Hormone Increased	6 (0.8%)	15 (2.0%)
Feeling Hot	2 (0.3%)	15 (2.0%)
Rhinorrhoea	8 (1.0%)	15 (2.0%)
Dermatitis Allergic	5 (0.6%)	13 (1.7%)
White Blood Cell Count Decreased	1 (0.1%)	13 (1.7%)
Dysaesthesia	5 (0.6%)	12 (1.6%)
Hypersensitivity	2 (0.3%)	11 (1.4%)
Weight Decreased	3 (0.4%)	11 (1.4%)
Otitis Media	1 (0.1%)	10 (1.3%)
Lymphocyte Count Decreased	1 (0.1%)	9 (1.2%)

In EVOLVE-MS-2, a total of 506 patients were randomized; 504 were dosed with at least one dose of study drug and included in the safety population: Vumerity (N = 253) or dimethyl fumarate (N = 251). Vumerity met the primary endpoint demonstrating a significant reduction in number of days with an Impact Scale (IGISIS, a patient self-assessment tool for GI symptom severity and impact) score of ≥2 relative to exposure (adjusted rate ratio [95% confidence internal] of 0.54 [0.39 – 0.75], p = 0.0003), representing a 46% reduction with Vumerity compared to dimethyl fumarate. In this study, overall adverse events were 34.8% and 49%, respectively. Treatment discontinuations were 1.6% and 6%, respectively, and the differences in these numbers were driven by discontinuations for GI tolerability reasons (0.8% and 4.8%,

respectively). Treatment-related adverse events of ≥5% for Vumerity or dimethyl fumarate, respectively, that demonstrated a numerical difference between the two groups of >2% were flushing (32.8% vs. 40.2%), diarrhea (13.8% vs. 18.7%), nausea (13.4% vs. 17.9%), upper abdominal pain (6.3% vs. 13.9%), abdominal pain (5.5% vs. 9.6%), vomiting (3.2% vs. 7.6%) [see Table 2].

Table 2: Adverse Reactions Reported for Vumerity and dimethyl fumarate in the 5-week EVOLVE-MS-2 Study

MedDRA	**Frequency**	
System Organ Class	**Vumerity N = 253 [%]**	**Dimethyl fumarate N = 251 [%]**
Vascular Disorders		
Flushing	32.8	40.2
Gastrointestinal Disorders		
Diarrhea	13.8	18.7
Nausea	13.4	17.9
Abdominal pain upper	6.3	13.9
Abdominal pain	5.5	9.6
Vomiting	3.2	7.6

Description of selected adverse reactions

The adverse reaction profile of Vumerity is expected to be similar to that of dimethyl fumarate.

Flushing

Flushing in treatment with Vumerity is expected to be similar to that seen with dimethyl fumarate. In the placebo-controlled studies, the incidence of flushing (35% versus 4%) and hot flushes (7% versus 2%) was increased in patients treated with dimethyl fumarate compared to placebo, respectively. Flushing is usually described as reddening or hot flush, but can include other adverse reactions (e.g. warmth, redness, itching, and burning sensation). The incidence of patients with flushing was higher early in the course of treatment (primarily during the first month) and decreased over time. In patients who experience flushing, these events may occur intermittently throughout treatment with dimethyl fumarate. In patients with flushing, the majority had flushing events that were mild or moderate in severity. Overall, 3% of patients treated with dimethyl fumarate discontinued due to flushing. Cases of serious flushing which may be

characterised by generalised erythema, rash and/or pruritus, were seen in less than 1% of patients treated with dimethyl fumarate (see section “Dosage and administration”). In clinical trials, 2 of the patients who reported serious flushing reactions presented similar symptoms to, and were treated as, hypersensitivity reactions (i.e. patients received anti-histamines and corticosteroids).

Gastrointestinal

GI tolerability in patients treated with Vumerity was directly compared to dimethyl fumarate in EVOLVE-MS-2. The incidence of gastrointestinal events (e.g. diarrhoea [13.8% vs. 18.7%], nausea [13.4% vs. 17.9%], upper abdominal pain [6.3% vs. 13.9%], abdominal pain [5.5% vs. 9.6%], and vomiting [3.2% vs. 7.6%]) was decreased in patients treated with Vumerity compared to dimethyl fumarate, respectively, in EVOLVE-MS-2. In this study, 0.8% (N = 2) treated with Vumerity discontinued treatment due to gastrointestinal events, as compared with 4.8% (N = 12) for dimethyl fumarate. There were no serious GI events for either Vumerity or dimethyl fumarate in this study.

The incidence of gastrointestinal adverse reactions (e.g. diarrhoea [14% vs. 11%], nausea [12% vs. 9%], upper abdominal pain [10% vs. 6%], abdominal pain [10% vs. 5%], vomiting [9% vs. 5%] and dyspepsia [5% vs. 3%]) was increased overall in patients treated with dimethyl fumarate compared to placebo, respectively (48% vs. 36%). The incidence of patients with gastrointestinal adverse reactions was higher early in the course of treatment (primarily during the first month) and decreased over time. In patients who experience gastrointestinal adverse reactions, these events may occur intermittently throughout treatment with dimethyl fumarate. Four percent (4%) of patients treated with dimethyl fumarate discontinued due to gastrointestinal adverse reactions. The incidence of serious gastrointestinal adverse reactions, including gastroenteritis and gastritis, was seen in less than 1% of patients treated with dimethyl fumarate.

Hepatic function

In placebo-controlled studies of dimethyl fumarate, elevations of hepatic transaminases were observed. The increased incidence of elevations of hepatic transaminases in patients treated with dimethyl fumarate relative to placebo was primarily seen during the first 6 months of treatment. The majority of patients with elevated hepatic transaminases had levels that were 3×

the upper limit of normal (ULN). Elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >1× ULN and <3× ULN occurred in 42% or in 24%, respectively, of patients taking dimethyl fumarate (vs. 31% or 19%, respectively, under placebo). Increases in ALT and AST by ≥ 3× ULN, respectively, were seen in 5% and 2% of patients treated with placebo and 6% and 2% of patients treated with dimethyl fumarate. There were no elevations in transaminases ≥3× ULN with concomitant elevations in total bilirubin >2× ULN. Discontinuations due to elevated hepatic transaminases were <1%, similar to the frequency seen in patients treated with dimethyl fumarate or placebo.
Liver function abnormalities (elevations in transaminases ≥3× ULN with concomitant elevations in total bilirubin >2× ULN) have been reported following dimethyl fumarate administration in the post marketing phase. These abnormalities resolved upon treatment discontinuation (see section “Warnings and precautions”).

Elevations in hepatic transaminases observed in EVOLVE-MS-2 were similar between Vumerity and dimethyl fumarate and similar to prior dimethyl fumarate studies. The majority of patients with elevated hepatic transaminases had levels that were <3× ULN and did not require dose adjustment or termination. Elevations in hepatic transaminases ≥3× ULN and ≥5× ULN, respectively, were seen in 0.8% (N = 2) and 0.4% (N = 1) of patients for Vumerity and 1.6% (N = 4) and 0.4% (N = 1) of patients for dimethyl fumarate. Treatment interruptions due to elevated hepatic transaminases were seen in 0.8% (N = 2) of patients treated with Vumerity and 0.4% (N = 1) of patients treated with dimethyl fumarate.

Renal

In placebo-controlled studies of dimethyl fumarate, the incidence of proteinuria was higher in patients treated with dimethyl fumarate (9%) compared to placebo (7%). The overall incidence of renal and urinary adverse reactions was similar for dimethyl fumarate and placebo-treated patients. There were no reports of serious renal failure. On urinalysis, the percentage of patients with protein values of 1+ or greater was similar for dimethyl fumarate (43%) and placebo-treated patients (40%). Typically, laboratory values for proteinuria were not progressive. Compared to patients treated with placebo, estimated glomerular filtration rate (eGFR) was observed to increase in patients treated with dimethyl fumarate, including those patients with 2 consecutive occurrences of proteinuria (≥1+).

Haematology

In the placebo-controlled studies of dimethyl fumarate, most patients (>98%) had normal lymphocyte values prior to initiating treatment. Upon treatment with dimethyl fumarate, 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 in 6% of patients treated with dimethyl fumarate. A lymphocyte count $<0.2 \times 10^9$/L was observed in 1 patient treated with dimethyl fumarate and in no patient treated with placebo. In clinical trials, 2% of patients had lymphopenia $<0.5 \times 10^9$/L for at least six months. In these patients, lymphocyte counts remained $<0.5\times 10^9$/L in the majority of controls when the therapy was continued.

In these studies, patients who discontinued dimethyl fumarate therapy with lymphocyte counts below the lower limit of normal (LLN) were monitored for recovery of lymphocyte counts to the LLN. A pooled subgroup analysis of patients with lymphocyte counts of $<0.5 \times 10^9$/L for six months or greater (2% of the total population) estimates the mean overall time to recover lymphocyte counts to LLN as 29 weeks (95% CI: 0, 61.1). For patients without prolonged severe lymphopenia, the analysis describes the mean time to recovery as 4.7 weeks (95% CI: 0, 16.2).

The incidence of infections (58% vs. 60%) and serious infections (2% vs. 2%) was similar in patients treated with placebo or dimethyl fumarate. An increased incidence of infections and serious infections was not observed in patients with lymphocyte counts $<0.8 \times 10^9$/L or 0.5×10^9/L. Progressive multifocal leukoencephalopathy occurred in the setting of prolonged severe lymphopenia.

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

Laboratory abnormalities

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

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

Post-marketing experience

Anaphylaxis and angioedema

In the post-marketing phase, allergic reactions such as anaphylaxis and angioedema with symptoms including urticaria, difficulty breathing and a swollen throat and tongue have been reported following dimethyl fumarate administration. As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy has occurred in patients with lymphopenia (with counts < 0.91×10^9/L) following dimethyl fumarate administration. These PML cases have occurred predominantly in the setting of prolonged moderate to severe lymphopenia. (See "Warnings and precautions").

Herpes zoster

Herpes zoster infection has been reported with dimethyl fumarate administration in the post-marketing phase. The majority of cases were non-serious. (See "Warnings and precautions").

Rhinorrhea and Alopecia

Rhinorrhea and alopecia have been reported with dimethyl fumarate administration in the post-marketing phase.

Overdose

Cases of overdose have been reported. The symptoms described in these cases were consistent with the known adverse event profile of Vumerity. The recommendation in the event of overdose of Vumerity is to observe and provide supportive care, as medically indicated. There are no known therapeutic interventions to enhance elimination of the drug nor is there a known antidote.

Reporting of suspected adverse reaction

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

Properties/Effects

ATC code

L04AX09

Mechanism of action

The pathophysiology of MS is multifaceted and propagated through ongoing inflammatory and neurodegenerative stimuli, mediated at least in part by toxic oxidative stress. Due to the similarities between Vumerity and dimethyl fumarate, Vumerity is assumed to have the same effects on MS pathophysiology as dimethyl fumarate.

Preclinical studies indicate that the pharmacodynamic effects of dimethyl fumarate and its metabolite monomethyl fumarate appear to be primarily mediated through activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway, which is the cellular defence system for responding to a variety of potentially toxic stimuli, including inflammatory and oxidative stress. Dimethyl fumarate has been shown to up regulate Nrf2-dependent antioxidant genes in patients (e.g. NAD(P)H dehydrogenase, quinone 1; [NQO1], confirming clinical pharmacodynamic activity in humans.

Dimethyl fumarate reduces inflammatory responses in both peripheral and central cells, and promotes cytoprotection of central nervous system cells against toxic stressors, demonstrating beneficial effects on pathways known to exacerbate multiple sclerosis pathology. Vumerity and dimethyl fumarate undergo rapid hydrolysis prior to systemic circulation by esterases and are converted to the primary active metabolite, monomethyl fumarate.
However, the mechanism by which Vumerity and dimethyl fumarate exerts therapeutic effects in multiple sclerosis is not fully understood.

Pharmacodynamics

Activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) Transcriptional Pathway
The mechanism of action of Vumerity and dimethyl fumarate appears to be mediated, at least in part, through activation of the Nrf2 anti-oxidant transcriptional pathway. Biological response markers of Nrf2 activation (e.g. NAD(P)H dehydrogenase, quinone 1 [NQO1]) are detected at elevated levels in blood from patients with MS following 12 or 48 weeks of oral dosing with dimethyl fumarate. These clinical data appear to be consistent with preclinical studies demonstrating dimethyl fumarate-dependent up-regulation of Nrf2 antioxidant response genes

in multiple tissue types. The relationships between blood NQO1 levels and the mechanism(s) by which dimethyl fumarate exerts its effects in MS are unknown.

Effects on the immune system

In preclinical and clinical studies, dimethyl fumarate demonstrates anti-inflammatory and immunomodulatory properties. Dimethyl fumarate and monomethyl fumarate, the primary metabolite of dimethyl fumarate, significantly reduce immune cell activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli in preclinical models, and moreover in clinical studies, affects lymphocyte phenotypes through a down-regulation of pro-inflammatory cytokine profiles (TH1, TH17), with a bias towards anti-inflammatory production (TH2). Dimethyl fumarate demonstrates therapeutic activity in multiple models of inflammatory and neuroinflammatory injury, and also appears to promote improvement in blood brain barrier integrity.
In Phase 3 studies, following treatment with dimethyl fumarate mean lymphocyte counts decreased on average by approximately 30% of their baseline value over the first year with a subsequent plateau. The anti-inflammatory and immune-modulatory effects appear consistent with the significant clinical activity of dimethyl fumarate in reducing brain lesions and relapses in multiple sclerosis patients.

Effects on the central nervous system

In preclinical studies, monomethyl fumarate is able to penetrate into the central nervous system where it promotes cyto- and neuro-protective responses. Dimethyl fumarate and monomethyl fumarate significantly improve cell viability after oxidative challenge in primary cultures of astrocytes and neurons, suggesting monomethyl fumarate and dimethyl fumarate directly prevent neurodegeneration in response to toxic stress. Acute neurotoxic injury models and genetic models of neurodegenerative disease confirm that dimethyl fumarate provides therapeutic benefit in reducing neuronal and functional damage resulting from various types of toxic stimuli and other forms of cellular stress inherent in neurodegenerative disease states. These preclinical data combined with imaging and functional endpoints from clinical studies suggest dimethyl fumarate and Vumerity may promote a neuroprotective benefit in the central nervous system.

Effects on the Gastrointestinal System

In a double-blind clinical study comparing GI tolerability of Vumerity versus dimethyl fumarate, Vumerity demonstrated reduced incidence of GI adverse events, as well as GI adverse events leading to treatment discontinuation, compared to dimethyl fumarate (see section “Undesirable effects”).

Effect on the Cardiovascular System

In a double-blind, placebo- and active-controlled thorough QT study in healthy subjects, Vumerity up to 2× the recommended doses (924 mg BID) did not have a clinically relevant effect on QTc interval.

Effects of the metabolite HES

2-Hydroxyethyl succinimide (HES) is a major inactive metabolite of Vumerity. In in vitro studies, HES demonstrated no biological activities at concentrations similar to or exceeding those seen clinically and was not shown to interfere with biological activity of monomethyl fumarate. To assess the potential impact of HES on efficacy in vivo, diroximel fumarate was tested compared to dimethyl fumarate in a standard rat model of MS and diroximel fumarate and dimethyl fumarate were found to have similar efficacy, demonstrating that HES does not interfere with efficacy in vivo. In the interim analysis of the ongoing, 96-week clinical study of Vumerity in patients with MS, HES did not appear to have any clinically relevant impact on the safety profile of Vumerity.

Clinical efficacy

Vumerity and dimethyl fumarate are rapidly metabolized by esterases before they reach the systemic circulation to the same active metabolite, monomethyl fumarate, following oral administration. The pharmacokinetics (PK) comparability of Vumerity to dimethyl fumarate through the analysis of monomethyl fumarate exposure has been demonstrated, thus their efficacy profiles are expected to be similar (see section “Pharmacokinetics”). The clinical studies described in the following sections were conducted using dimethyl fumarate.

Two, 2-year, randomised, double-blind, placebo controlled studies [DEFINE, 1’234 subjects and CONFIRM, 1’417 subjects] and an 8-year two phase extension study [ENDORSE, 1’736 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 was demonstrated in two of the three studies (DEFINE and CONFIRM) including 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 who, within 6 weeks of randomisation, had a brain Magnetic Resonance Imaging (MRI) scan demonstrating at least 1 gadolinium-enhancing (Gd+) lesion.

In DEFINE and CONFIRM, dimethyl fumarate was investigated either at a dose of 240 mg twice a day or 240 mg three times a day (DEFINE: 410 patients twice and 416 patients three times a day; CONFIRM: 359 patients twice and 345 patients three times a day). The efficacy of both dosages was comparable: efficacy was no better with lower tolerance of the higher dosage. CONFIRM contained a rater-blinded (i.e. study physician/investigator assessing the response to study treatment is blinded, but not the patient or treating physician) reference comparator of glatiramer acetate.

Median values for baseline characteristics in DEFINE: age 39 years, years since diagnosis 4.0 years and EDSS score at baseline 2.0. Median values for baseline characteristics in CONFIRM: age 37 years, years since diagnosis 3.0 years and EDSS score at baseline 2.5.

Compared to placebo, patients treated with dimethyl fumarate had a statistically significant reduction in the primary endpoint in DEFINE (proportion of subjects who had had a relapse at 2 years) and the primary endpoint in CONFIRM (annualised relapse rate at 2 years).

Dimethyl fumarate only exhibited a statistically significant reduction in the progression of disability after 12 weeks in DEFINE, and not in CONFIRM. When considering progression of disability after 24 weeks, neither study revealed a statistically significant reduction.

Table 3: Clinical results of DEFINE and CONFIRM

	DEFINE		**CONFIRM**		
	Placebo	**Dimethyl fumarate 240 mg twice a day**	**Placebo**	**Dimethyl fumarate 240 mg twice a day**	**Glatiramer acetate**
Clinical Endpoints[a]					

	DEFINE		CONFIRM		
	Placebo	**Dimethyl fumarate 240 mg twice a day**	**Placebo**	**Dimethyl fumarate 240 mg twice a day**	**Glatiramer acetate**
No. of 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 of patients with one relapse	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 of patients 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 of patients 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. of 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)

[a]All analyses of clinical endpoints were intent-to-treat analyses;

[b]MRI analysis used MRI cohort

*P-value < 0.05;

**P-value < 0.01;

***P-value < 0.0001;
#not statistically significant

ENDORSE enrolled eligible patients from DEFINE and CONFIRM into an 8-year two phase extension study of 1’736 patients with RRMS. The first phase was a multicenter, parallel group, randomized, dose blind, dose comparison study in which patients received dimethyl fumarate at a dose of 240 mg twice a day or 240 mg three times a day. The second phase was an open label study during which all patients received dimethyl fumarate at a dose of 240 mg twice a day. Eligible patients were enrolled at the Week 96 visit (Visit 24) of their previous study (DEFINE or CONFIRM), which served as the Baseline Visit for this extension study.

The primary objective of ENDORSE was to evaluate the long-term safety of dimethyl fumarate. The secondary objectives were to evaluate the long-term efficacy of dimethyl fumarate using clinical endpoints (including relapse and ARR) and disability progression (EDSS) and in terms of MS brain lesions on MRI scans.
The median age of patients was 40.0 years. Most patients (945 participants, 54%) were in the study for 7 years or longer and the median time spent in the study (min, max) was 6.759 (0.04, 10.98) years.

In the first year of treatment with dimethyl fumarate twice daily in ENDORSE, the adjusted ARR (95% CI) ranged from 0.139 (0.105, 0.184) to 0.178 (0.108, 0.295), and remained low in the eighth year, ranging from 0.077 (0.039, 0.153) to 0.111 (0.053, 0.233) (see Table 3).

Table 3: Adjusted ARR at Year 1 and Year 8 for patients treated twice a day in the ENDORSE study

	Overall population (N=868)		
Clinical Endpoint (previously treated with)	**dimethyl fumarate BID** (dimethyl fumarate BID in DEFINE/ CONFIRM) N=501	**dimethyl fumarate BID** (placebo in DEFINE/ CONFIRM) N=249	**dimethyl fumarate BID** (GA in DEFINE/ CONFIRM) N=118
Adjusted ARR (95% CI) **Year 1**[a]	0.139 (0.105, 0.184)	0.171 (0.119, 0.248)	0.178 (0.108, 0.295)
Adjusted ARR (95% CI) **Year 8**[b]	0.110 (0.073, 0.165) n=261	0.077 (0.039, 0.153) n=111	0.111 (0.053, 0.233) n=55

[a] From a negative binomial regression model, adjusted for baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40), region and number of relapses in the 1 year prior to DEFINE/CONFIRM study entry.

[b] From a Poisson regression model, adjusted for baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40), region and number of relapses in the 1 year prior to DEFINE/CONFIRM study entry.

In the ENDORSE study, the mean (median) EDSS score at baseline in the twice a day group ranged from 2.42 (2.00) to 2.64 (2.0). The estimated proportion of patients with confirmed disability progression (95% CI) from the start of ENDORSE up to the eighth year of ENDORSE after treatment with dimethyl fumarate twice daily ranged from 0.326 (0.279, 0.380) to 0.343 (0.272, 0.427). Table 4 shows the EDSS at baseline and Week 384.

Table 4: Mean EDSS score at Baseline and Week 384 for patients treated twice a day in the ENDORSE study

	Overall Population (N=868)		
Clinical Endpoint (previously treated with)	**dimethyl fumarate BID** dimethyl fumarate BID in DEFINE/ CONFIRM) N=501	**dimethyl fumarate BID** Placebo in DEFINE/ CONFIRM) N=249	**dimethyl fumarate BID** GA in DEFINE/ CONFIRM) N=118
Mean EDSS score (Median) **Baseline**	2.42 (2.0)	2.58 (2.5)	2.64 (2.0)
Mean EDSS score (Median) **Week 384**	2.64 (2.5) n=230	2.87 (2.5) n=101	3.03 (3.0) n=45

In the ENDORSE study, 752 patients (367 in the twice a day group) were included in an MRI cohort, which also included patients who had previously been included in the MRI cohort of DEFINE or CONFIRM. Due to sample size restrictions, MRI results are presented only through Year 6 of ENDORSE. The percentage of patients at Year 6 with no Gd+ lesions ranged from 90% to 100%. The mean number of new T1 hypointense lesions over 6 years, adjusted for

region and baseline volume of T1 lesions (based on negative binomial regression), ranged from 1.060 (1.0) to 3.419 (2.0).

Pharmacokinetics

Following oral administration Vumerity (diroximel fumarate) undergoes rapid presystemic hydrolysis by esterases and is converted into both its active primary metabolite, monomethyl fumarate, and an inactive metabolite, HES. Diroximel fumarate is not quantifiable in plasma following oral administration of Vumerity. Therefore, all pharmacokinetic analyses related to Vumerity were performed with plasma monomethyl fumarate concentrations.
Pharmacokinetic data were obtained in subjects with multiple sclerosis and healthy volunteers.

Absorption

The median T_{max} of monomethyl fumarate is 2.5 to 3 hours. Following administration of Vumerity 462 mg twice a day in MS patients (A301), the mean C_{max} of monomethyl fumarate was 2.11 mg/L. The mean steady state daily AUC (AUC_{ss}) of monomethyl fumarate was estimated to be 8.32 mg*hr/L in MS patients.

Food Effect

Administration of Vumerity together with a high-fat, high-calorie meal (up to 1050 kcal and 55 g fat) did not affect the AUC of monomethyl fumarate, but resulted in an approximately 44% reduction in C_{max} compared to a fasting state. The monomethyl fumarate C_{max} with low-fat (up to 400 kcal and 15 g fat) and medium-fat meals (up to 700 kcal and 30 g fat) was reduced by approximately 12% and 25%, respectively.

Alcohol Effect

Co-administration of Vumerity with 5% v/v and 40% v/v ethanol did not alter total monomethyl fumarate exposure relative to administration with water, demonstrating that the co-ingestion of ethanol does not induce dose dumping. The mean peak plasma monomethyl fumarate concentration for diroximel fumarate was decreased by 9% and 21%, when co-administered with 240 mL of 5% v/v and 40% v/v of ethanol, respectively.

Distribution

The apparent volume of distribution (Vd) for monomethyl fumarate is 72-83 L in healthy subjects after administration of Vumerity. Human plasma protein binding of monomethyl fumarate is 27-45% and was not concentration dependent.

Metabolism

In humans, diroximel fumarate is extensively metabolized by esterases, which are ubiquitous in the gastrointestinal tract, blood, and tissues, before it reaches the systemic circulation. Esterase metabolism of diroximel fumarate produces both monomethyl fumarate, the active metabolite, and HES, an inactive metabolite.
Further metabolism of monomethyl fumarate occurs through esterases followed by the tricarboxylic acid (TCA) cycle, with no involvement of the cytochrome P450 (CYP) system. Fumaric and citric acid, and glucose are the major metabolites of monomethyl fumarate in plasma.

Elimination

Monomethyl fumarate is mainly eliminated as carbon dioxide in expired air with only trace amounts recovered in urine. The terminal half-life ($t_{1/2}$) of monomethyl fumarate is approximately 1 hour, and no accumulation in monomethyl fumarate plasma exposures occurred with multiple doses of Vumerity. HES is mainly eliminated in urine (58-63% of the dose).
Linearity

Vumerity exposure increases in an approximately dose-proportional manner in the recommended daily dose range (462 mg to 924 mg).

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 relapsing-remitting multiple sclerosis (RRMS) subjects, but did not affect safety and efficacy measures evaluated in the clinical studies.
Gender and age did not have a clinically significant impact on the pharmacokinetics of dimethyl fumarate. The pharmacokinetics in patients aged 65 and over have not been studied.

Paediatric population

The pharmacokinetics in patients below the age of 18 have not been studied.

Patients with renal impairment

A single-dose clinical study investigating the effect of renal impairment on the PK of the Vumerity metabolites monomethyl fumarate and HES was conducted. The study included cohorts with mild, moderate, and severe renal impairment and a healthy cohort and found no clinically relevant changes in monomethyl fumarate exposure. HES exposure increased 1.3-, 1.8-, and 2.7-fold with mild, moderate, and severe renal impairment, respectively. There are no data available on long-term use of Vumerity in patients with moderate or severe renal impairment.

Patients with hepatic impairment

No studies have been carried out on the pharmacokinetics in individuals with hepatic impairment.

Preclinical data

Mutagenesis

Diroximel fumarate was not mutagenic in the in vitro bacterial reverse mutation assay. Diroximel fumarate was clastogenic in the in vitro chromosomal aberration assay in human peripheral blood lymphocytes, but not clastogenic/genotoxic in vivo in the rat micronucleus and comet assays.

Carcinogenicity

Oral administration of diroximel fumarate (0, 0, 30, 100, 300 or 1000 [females only] mg/kg/day) for 26 weeks to Tg.rasH2 mice resulted in no drug-related tumours. At the highest dose tested, plasma exposures for MMF and HES (the major circulating drug-related compound in humans) were 3-13 (MMF) and 1-4 (HES) times those in humans at the recommended human dose (RHD) of 924 mg/day.

Oral administration of diroximel fumarate (0, 0, 15, 50, or 150 mg/kg/day) to male and female rats resulted in an increase in tumours (Leydig cell adenomas of the testes) in males at the highest dose tested. At the higher dose (50 mg/kg/day) that was not associated with drug-related tumours, plasma exposures for MMF and HES were similar to (MMF) and less than (HES) those in humans at the recommended human dose (RHD) of 924 mg/day.

Toxicology

Kidney toxicity was observed following repeated oral administration of diroximel fumarate to rats and monkeys. Renal findings included tubular degeneration/necrosis with regeneration, tubular hypertrophy and/or interstitial fibrosis, increased kidney weights, and functional changes in clinical pathology parameters (urine volume, specific gravity, and biomarkers of kidney injury). In the chronic toxicology studies, adverse renal findings occurred at monomethyl fumarate exposures that were approximately ≥1 times and ≥2.6 times, in rats and monkeys respectively, the exposure at the RHD of diroximel fumarate based on the AUC.

Gastrointestinal toxicity in mice and rats consisted of mucosal hyperplasia and hyperkeratosis in the forestomach and duodenum and was seen at exposures that were 11 times and 3 times, in mice and rats respectively, the exposure at the RHD of diroximel fumarate based on the AUC. The forestomach of mice and rats does not have a human counterpart.

Heart toxicity consisting of cardiac inflammation and necrosis was seen in three male rats in the 91-day rat study at exposures 4 times the exposure at the RHD of diroximel fumarate based on the AUC. These findings were not seen in the longer duration chronic rat study.

Bone toxicity consisting of partially-reversible damage to the epiphyseal plate of the proximal and distal femur and proximal tibia was seen in monkeys in the 91-day study at exposures of 15 times the exposure at the RHD of diroximel fumarate based on the AUC. These findings were not seen in the longer duration chronic monkey study. Decreased femur size, mass, density, and changes in bone geometry were observed along with lower body weights in juvenile rats administered diroximel fumarate from postnatal day (PND) 25 through PND 63. The bone toxicity in juvenile rats was adverse at exposures at least 6 times the RHD exposure of diroximel fumarate based on the AUC.

Testicular toxicity consisting of minimal germinal epithelial degeneration, increased incidence of giant spermatids, slight decrease in spermatids in the tubular epithelium, and decrease in testes weight was observed in CByB6F1 mice (wild type littermates of rasH2 mice) in a 28-day study. These findings occurred at exposures 15 times the exposure at the RHD of diroximel fumarate based on the AUC.

Reproductive toxicity

No adverse effects on fertility were observed following oral administration of diroximel fumarate to male rats (0, 40, 120, or 400 mg/kg/day) prior to and during mating with untreated females and, in a separate study, to female rats (0, 40, 120, or 450 mg/kg/day) prior to and during mating with untreated males and continuing to Gestation Day (GD) 7. At the highest doses tested, plasma exposures (AUC) for MMF were approximately 7-9 times that in humans at the RHD. Plasma levels of HES were not quantitated.

Oral administration of diroximel fumarate (0, 40, 100, or 400 mg/kg/day) to pregnant rats throughout organogenesis resulted in a decrease in fetal body weight and an increase in fetal skeletal variations at the highest dose tested, which was associated with maternal toxicity. Plasma exposures (AUC) for MMF and HES (the major circulating drug-related compound in humans) at the no-effect dose (100 mg/kg/day) for adverse effects on embryofetal development were approximately 2 times those in humans at the recommended human dose (RHD) of 924 mg/day.

Oral administration of diroximel fumarate (0, 50, 150, or 350 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in an increase in fetal skeletal malformations at the mid and high doses and reduced fetal body weight and increases in embryofetal death and fetal skeletal variations at the highest dose tested. The mid and high doses were associated with maternal toxicity. Plasma exposures (AUC) for MMF and HES at the no-effect dose (50 mg/kg/day) for adverse effects on embryofetal development were similar to (MMF) or less than (HES) those in humans at the RHD.

Oral administration of diroximel fumarate (0, 40, 100, or 400 mg/kg/day) to rats throughout gestation and lactation resulted in reduced weight, which persisted into adulthood, and adverse effects on neurobehavioral function in offspring at the highest dose tested. Plasma exposures (AUC) for MMF and HES at the no-effect dose for adverse effects on postnatal development (100 mg/kg/day) were approximately 3 times (MMF) or similar to (HES) those in humans at the RHD.

Other information

Shelf life

The expiery date of the product is indicated on the packaging materials.

Special precautions for storage

Keep out of the reach of children.

Store below 25°C and store in the original package.

Pharmaceutical particulars:

Excipients

Methacrylic Acid andEthyl acrylate copolymer
Crospovidone
Microcrystalline cellulose,
Colloida silicon dioxide
Triethyl citrate
Talc
Magnesium stearate, non-bovine

Capsule shell

Hypromellose
Titanium dioxide
Potassium chloride
Carrageenan
Water

Composition of Black ink SW-9008

Black iron Oxide
Shellac
Dehydrated Alcohol
Propylene Glycol
Isopropyl Alcohol
Butyl Alcohol
Ammonia Solution
Potassium Hydroxide
Purified water

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REGISTRATION NUMBER:

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