ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vumerity 231 mg gastro-resistant hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant hard capsule contains 231 mg diroximel fumarate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant hard capsule

White capsule, size 0 (approximately 18 mm in length), printed with 'DRF 231 mg' in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vumerity 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 231 mg twice a day. After 7 days, the dose should be increased to the recommended maintenance dose of 462 mg twice a day (see section 4.4).

Temporary dose reductions to 231 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended dose of 462 mg twice a day should be resumed.

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

Special populations

Elderly

Based on uncontrolled study data, the safety profile of diroximel fumarate in patients ≥55 years of age seems to be comparable to patients <55 years of age. Clinical studies with diroximel fumarate had limited exposure to patients aged 65 years and above and did not include sufficient numbers of patients aged 65 years and above to determine whether they respond differently than younger patients (see section 5.2). Based on the mechanism of action of the active substance there are no theoretical reasons for any requirement for dose adjustments in the elderly.

Renal impairment

No dose adjustment is necessary in patients with renal impairment (see section 5.2). Long-term safety of diroximel fumarate has not been studied in patients with moderate or severe renal impairment (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is necessary for patients with hepatic impairment (see sections 4.4 and 5.2). Diroximel fumarate has not been studied in patients with hepatic impairment.

Paediatric population

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

There is no relevant use of Vumerity in children aged less than 10 years for the indication of relapsing remitting multiple sclerosis.

Method of administration

For oral use.

Vumerity should be swallowed whole and intact. The capsules should not be crushed or chewed and the contents should not be sprinkled on food because the enteric-coating of the capsule contents prevents irritant effects on the gut.

Vumerity can be taken with or without food (see section 5.2). For those patients who may experience flushing or gastrointestinal adverse reactions, taking with food may improve tolerability (see sections 4.4 and 4.8).

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or other fumaric acid esters (see section 4.5).
Suspected or confirmed Progressive Multifocal Leukoencephalopathy (PML).

4.4 Special warnings and precautions for use

Diroximel fumarate and dimethyl fumarate are metabolised to monomethyl fumarate upon oral administration (see section 5.2). The risks associated with diroximel fumarate are expected to be similar to those reported for dimethyl fumarate even though not all the risks listed below have been observed specifically for diroximel fumarate.

Blood/laboratory tests

Changes in renal laboratory tests have been seen in clinical trials in patients 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 with Vumerity, 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 x upper limit of normal (ULN)) and elevation of total bilirubin levels (≥ 2 x 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 diroximel fumarate may develop lymphopenia (see section 4.8). Prior to initiating treatment, a current complete blood count, including lymphocytes, must be performed. If the lymphocyte count is found to be below the normal range, a thorough assessment of possible causes should be completed prior to initiation of treatment. Vumerity has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients. Treatment 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:

- Treatment 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 to $< 0.8 \times 10^9$/L for more than 6 months, the benefit/risk of treatment should be re-assessed.
- In patients with lymphocyte counts below 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).

Lymphocyte counts should be followed until recovery (see section 5.1). Upon recovery and in the absence of alternative treatment options, decisions about whether or not to restart Vumerity after treatment discontinuation should be based on clinical judgement.

Magnetic resonance imaging (MRI)

Before initiating treatment, 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 dimethyl fumarate (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 lower limit of normal [LLN]). Prolonged moderate to severe lymphopenia appears to increase the risk of PML with dimethyl fumarate, 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 Vumerity therapy. Cases of PML have occurred after approximately 1 to 5 years of dimethyl fumarate 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 defense (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, Vumerity 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 or 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.

If a patient develops PML, Vumerity must be permanently discontinued.

Prior treatment with immunosuppressive or immunomodulating therapies

No studies have been performed evaluating the efficacy and safety of diroximel fumarate when switching patients from other disease modifying therapies. The contribution of prior immunosuppressive therapy to the development of PML 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 dimethyl fumarate occurred in patients with prior immunomodulatory treatment.

When switching patients from another disease modifying therapy to Vumerity, the half-life and mechanism 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 treatment initiation and regularly during treatment (see Blood/laboratory tests above).

Severe renal impairment

The long-term safety of diroximel fumarate has not been studied in patients with moderate or severe renal impairment. Therefore, caution should be used when considering treatment in these patients (see sections 4.2 and 5.2).

Severe hepatic impairment

Diroximel fumarate has not been studied in patients with severe hepatic impairment. Therefore, caution should be used when considering treatment in these patients (see sections 4.2 and 5.2).

Severe active gastrointestinal disease

Diroximel fumarate has not been studied in patients with severe active gastrointestinal disease. Therefore, caution should be used when considering treatment in these patients.

Flushing

In dimethyl fumarate pivotal 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 adverse reactions were not life-threatening but led to hospitalisation. Prescribers and patients should be alert to this possibility in the event of severe flushing reactions with Vumerity (see sections 4.2, 4.5 and 4.8).

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.

Anaphylactic reactions

Cases of anaphylaxis/anaphylactoid reaction have been reported following dimethyl fumarate 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 Vumerity and seek immediate medical care if they experience signs or symptoms of anaphylaxis. Treatment should not be restarted (see section 4.8).

Infections

In the phase 3 placebo-controlled studies with dimethyl fumarate, the incidence of infections (60% versus 58%) and serious infections (2% versus 2%) was similar in patients treated with dimethyl fumarate or placebo, respectively.

Diroximel fumarate exerts immunomodulatory properties (see section 5.1).

Patients receiving Vumerity should be instructed to report symptoms of infections to a physician. If a patient develops a serious infection, suspending treatment should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Patients with serious infections should not start treatment until the infection(s) is resolved.

There was no increased incidence of serious infections observed in patients treated with dimethyl fumarate with lymphocyte counts $< 0.8 \times 10^9$/L or $< 0.5 \times 10^9$/L. If Vumerity 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 subsection on PML).

Herpes zoster infections

Cases of herpes zoster have occurred with diroximel fumarate and dimethyl fumarate. The majority of cases with dimethyl fumarate 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. Patients should be monitored 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. Withholding treatment should be considered in patients with serious infections until the infection has resolved (see section 4.8).

Treatment initiation

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 Vumerity 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

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

Vumerity should not be administered concomitantly with dimethyl fumarate.

Potential interaction risks were not identified from *in vitro* and/or *in vivo* inhibition studies of transporters, from *in vitro* CYP-inhibition and induction studies, or studies of the protein binding of diroximel fumarate and its major metabolites, active metabolite monomethyl fumarate (MMF) and inactive metabolite 2-hydroxyethyl succinimide (HES).

Although not studied with diroximel fumarate, *in vitro* CYP induction studies did not demonstrate an interaction between dimethyl fumarate and oral contraceptives. In an *in vivo* study, co-administration of dimethyl fumarate 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 diroximel fumarate on their exposure is not expected.

Diroximel fumarate has not been studied in combination with anti-neoplastic or immunosuppressive therapies and caution should, therefore, be used during concomitant administration. In MS 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 Vumerity therapy. In a clinical study involving a total of 71 patients with relapsing remitting multiple sclerosis (RRMS), patients on dimethyl fumarate 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 titre) 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 titre to the three vaccines, was achieved by fewer patients 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 Vumerity. Live vaccines might carry an increased risk of clinical infection and should not be given to patients unless, in exceptional cases, this potential risk is considered to be outweighed by the risk to the individual of not vaccinating.

Evidence from healthy volunteer studies suggests that dimethyl fumarate-associated flushing is likely to be prostaglandin mediated. In two healthy volunteer studies with dimethyl fumarate, the

administration of 325 mg (or equivalent) non enteric coated acetylsalicylic acid, 30 minutes prior to dimethyl fumarate, dosing over 4 days and over 4 weeks, respectively, did not alter the pharmacokinetic profile of dimethyl fumarate. Potential risks associated with acetylsalicylic acid therapy should be considered prior to co-administration with Vumerity 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 Vumerity (see section 4.4).

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 diroximel fumarate in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Vumerity is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception (see section 4.5). Vumerity 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 diroximel 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 Vumerity therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of Vumerity on human fertility. Data from animal studies with diroximel fumarate showed no impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Vumerity has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Upon oral administration, diroximel fumarate and dimethyl fumarate are rapidly metabolised to monomethyl fumarate before they reach the systemic circulation, adverse reactions are similar once metabolised.

The most common adverse reactions for dimethyl fumarate were flushing (35%) and gastrointestinal events (i.e. diarrhoea 14%, nausea 12%, abdominal pain 10% and abdominal pain upper 10%). The most commonly reported adverse reactions leading to discontinuation in patients treated with dimethyl fumarate were flushing (3%) and gastrointestinal events (4%).

Tabulated list of adverse reactions

The adverse reactions which were more frequently reported in dimethyl fumarate-treated patients as compared to placebo-treated patients from two pivotal phase 3 placebo controlled clinical trials and post marketing experience are presented in Table 1.

The adverse reactions are presented as MedDRA preferred terms under the MedDRA system organ class (SOC). The incidence of the adverse reactions below is expressed according to the following categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (frequency cannot be estimated from the available data).

Table 1: Adverse reactions

MedDRA System Organ Class	Adverse reaction	Frequency category
Infections and infestations	Gastroenteritis	Common
	Progressive multifocal leukoencephalopathy (PML)[1]	Not known
	Herpes zoster[1]	Not known
Blood and lymphatic system disorders	Lymphopenia[1, 2]	Common
	Leukopenia	Common
	Thrombocytopenia	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylaxis	Not known
	Dyspnoea	Not known
	Hypoxia	Not known
	Hypotension	Not known
	Angioedema	Not known
Nervous system disorders	Burning sensation	Common
Vascular disorders	Flushing[1]	Very common
	Hot flush	Common
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Not known
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[1]	Common
	Alanine aminotransferase increased[1]	Common
	Drug-induced liver injury	Not known
Skin and subcutaneous tissue disorders	Pruritus	Common
	Rash	Common
	Erythema	Common
	Alopecia	Common
Renal and urinary disorders	Proteinuria	Common
General disorders and administration site conditions	Feeling hot	Common

MedDRA System Organ Class	Adverse reaction	Frequency category
Investigations	Ketones measured in urine	Very common
	Albumin urine present	Common
	White blood cell count decreased	Common

[1] See 'Description of selected adverse reactions' for further information

[2] Lymphopenia was reported with the frequency "very common" in a phase 3, open-label, uncontrolled study with diroximel fumarate

Description of selected adverse reactions

Flushing

In the placebo-controlled dimethyl fumarate studies, the incidence of flushing (34% versus 5%) and hot flush (7% versus 2%) was increased in patients treated with dimethyl fumarate 240 mg twice daily 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 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. 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 dimethyl fumarate (see sections 4.2, 4.4 and 4.5).

In the diroximel fumarate phase 3 double-blind trial (see section 5.1), flushing and hot flush were reported in 32.8% and 1.6% of diroximel fumarate-treated patients and in 40.6% and 0.8% of dimethyl fumarate-treated patients. There were no serious events of flushing or discontinuations due to flushing.

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 dimethyl fumarate 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 dimethyl fumarate. In the majority of patients who experienced gastrointestinal events, it was mild or moderate in severity. Four per cent (4%) of patients treated with dimethyl fumarate discontinued due to gastrointestinal events. The incidence of serious gastrointestinal events, including gastroenteritis and gastritis, was seen in 1% of patients treated with dimethyl fumarate (see section 4.4).

Gastrointestinal adverse reactions reported in the clinical study with diroximel fumarate and dimethyl fumarate are presented in section 5.1.

Hepatic function

Based on data from placebo-controlled studies with dimethyl fumarate, 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 dimethyl fumarate relative to placebo was primarily seen during the first 6 months of treatment. Elevations of alanine aminotransferase and aspartate aminotransferase ≥ 3 x ULN, respectively, were seen in 5% and 2% of patients treated with placebo and 6% and 2% of patients treated with dimethyl fumarate. Discontinuations due to elevated hepatic transaminases were < 1% and similar in patients treated with dimethyl fumarate or placebo. Elevations in transaminases ≥ 3 x ULN with concomitant elevations in total bilirubin > 2 x ULN indicative of drug-induced liver injury were not observed during placebo-controlled studies, but have been reported in post marketing experience following dimethyl fumarate administration, which resolved upon treatment discontinuation.

Lymphopenia

In the diroximel fumarate phase 3, open-label, uncontrolled trial, treatment was discontinued in patients with confirmed lymphocyte counts < 0.5 x 10^9/L which persisted for ≥ 4 weeks.

In the placebo-controlled studies for 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 x 10^9/L were observed in < 1% of patients treated with placebo and 6% of patients treated with dimethyl fumarate. A lymphocyte count < 0.2 x 10^9/L was observed in 1 patient treated with dimethyl fumarate and in no patients treated with placebo.

In clinical studies (both controlled and uncontrolled), 41% of patients treated with dimethyl fumarate had lymphopenia (defined in these studies as < 0.91 x 10^9/L). Mild lymphopenia (counts ≥ 0.8 x 10^9/L to < 0.91 x 10^9/L) was observed in 28% of patients; moderate lymphopenia (counts ≥ 0.5 x 10^9/L to < 0.8 x 10^9/L) persisting for at least six months was observed in 11% of patients; severe lymphopenia (counts < 0.5 x 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 x 10^9/L with continued therapy.

In addition, in an uncontrolled, prospective, post-marketing study, at week 48 of treatment with dimethyl fumarate (n=185) CD4+ T cells were moderately (counts ≥ 0.2 x 10^9/L to < 0.4 x 10^9/L) or severely (< 0.2 x 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 x 10^9/L and 25% of patients at counts < 0.1 x 10^9/L.

In controlled and uncontrolled clinical studies, patients who discontinued dimethyl fumarate therapy with lymphocyte counts below the lower limit of normal (LLN) were monitored for recovery of lymphocyte count to the LLN (see section 5.1).

Infections, including PML and opportunistic infections

Cases of infections with JCV causing PML have been reported with dimethyl fumarate (see section 4.4). PML may be fatal or result in severe disability. In one of the clinical trials, one patient taking dimethyl fumarate developed PML in the setting of prolonged severe lymphopenia (lymphocyte counts predominantly < 0.5 x 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 x 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 x 10^9/L, whereas reductions in CD4+ T cells counts were variable (ranging from < 0.05 to 0.5 x 10^9/L) and correlated more with the overall severity of lymphopenia (< 0.5 x 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 dimethyl fumarate and likewise diroximel fumarate, however, PML also occurred in patients treated with dimethyl fumarate 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 dimethyl fumarate use. In the long-term extension study, in which 1,736 MS patients were treated with dimethyl fumarate, 5% experienced one or more events of herpes zoster, the majority of which were mild to moderate in severity. Most patients, including those who experienced a serious herpes zoster infection, had lymphocyte counts above the lower limit of normal. In a majority of patients 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 absolute lymphocyte count (ALC) in patients with herpes zoster infection in the post-marketing setting. However, when reported, most patients experienced moderate ($\geq 0.5 \times 10^9$/L to $< 0.8 \times 10^9$/L) or severe ($< 0.5 \times 10^9$/L to 0.2×10^9/L) lymphopenia (see section 4.4).

Laboratory abnormalities

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

Levels of 1,25-dihydroxyvitamin D decreased in dimethyl fumarate 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 dimethyl fumarate 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 dimethyl fumarate therapy.

Paediatric population

The safety of Vumerity in paediatric patients has not yet been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In reported cases of overdose, the symptoms described were consistent with the known adverse reaction profile of the product. There are no known therapeutic interventions to enhance elimination of diroximel fumarate 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: Immunosuppressants, other immunosuppressants. ATC code: L04AX09

Mechanism of action

The mechanism by which diroximel fumarate exerts therapeutic effects in MS is not fully understood. Diroximel fumarate acts via the major active metabolite, monomethyl fumarate. Preclinical studies indicate that the pharmacodynamic responses of monomethyl fumarate appears to be mediated, at least in part, 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.

Pharmacodynamic effects

Effects on Immune System

In clinical studies, dimethyl fumarate demonstrated anti-inflammatory and immunomodulatory properties. Dimethyl fumarate and monomethyl fumarate (the active metabolite of diroximel fumarate and dimethyl fumarate) significantly reduce immune cell activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli and moreover affect lymphocyte phenotypes through a down-regulation of pro-inflammatory cytokine profiles (T_H1, T_H17), and biased towards anti-inflammatory production (T_H2). In phase 3 studies in MS patients (DEFINE, CONFIRM and ENDORSE), upon 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. In these studies, patients who discontinued dimethyl fumarate therapy with lymphocyte counts below the lower limit of normal (LLN, 910 cells/mm^3) were monitored for recovery of lymphocyte counts to the LLN.

Figure 1 shows the proportion of patients estimated to reach the LLN based on the Kaplan-Meier method without prolonged severe lymphopenia. The recovery baseline (RBL) was defined as the last on-treatment ALC prior to dimethyl fumarate discontinuation. The estimated proportion of patients recovering to LLN (ALC ≥ 0.9 x 10^9/L) at Week 12 and Week 24, who had mild, moderate, or severe lymphopenia at RBL are presented in Table 2, Table 3, and Table 4 with 95% pointwise confidence intervals. The standard error of the Kaplan-Meier estimator of the survival function is computed using Greenwood's formula.

Figure 1: Kaplan-Meier Method; Proportion of Patients with Recovery to ≥ 910 cells/mm^3 LLN from the Recovery Baseline (RBL)

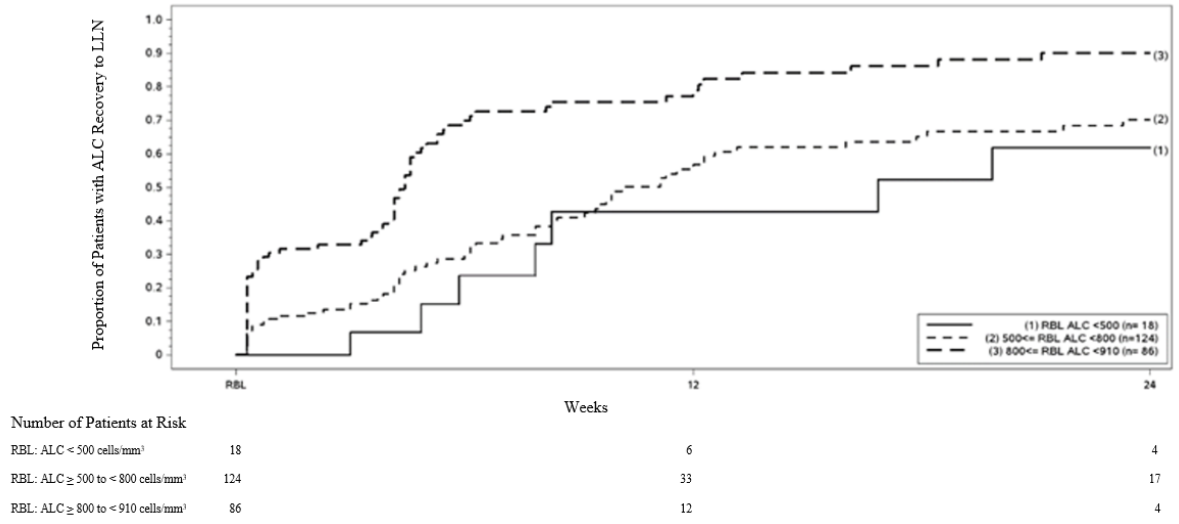

Table 2: Kaplan-Meier Method; Proportion of patients estimated to reach LLN, mild lymphopenia at the recovery baseline (RBL), excluding patients with prolonged severe lymphopenia

Number of patients with mild lymphopenia[a] at risk	**Baseline N=86**	**Week 12 N=12**	**Week 24 N=4**
Proportion reaching LLN (95% CI)		0.81 (0.71, 0.89)	0.90 (0.81, 0.96)

[a] Patients with ALC < 910 and ≥ 800 cells/mm^3 at RBL, excluding patients with prolonged severe lymphopenia.

Table 3: Kaplan-Meier Method; Proportion of patients estimated to reach LLN, moderate lymphopenia at the recovery baseline (RBL), excluding patients with prolonged severe lymphopenia

Number of patients with moderate lymphopenia[a] at risk	Baseline N=124	Week 12 N=33	Week 24 N=17
Proportion reaching LLN (95% CI)		0.57 (0.46, 0.67)	0.70 (0.60, 0.80)

[a] Patients with ALC < 800 and ≥ 500 cells/mm^3 at RBL, excluding patients with prolonged severe lymphopenia.

Table 4: Kaplan-Meier Method; Proportion of patients estimated to reach LLN, severe lymphopenia at the recovery baseline (RBL), excluding patients with prolonged severe lymphopenia

Number of patients with severe lymphopenia[a] at risk	Baseline N=18	Week 12 N=6	Week 24 N=4
Proportion reaching LLN (95% CI)		0.43 (0.20, 0.75)	0.62 (0.35, 0.88)

[a] Patients with ALC < 500 cells/mm^3 at RBL, excluding patients with prolonged severe lymphopenia.

Clinical efficacy and safety

Diroximel fumarate and dimethyl fumarate are rapidly metabolised by esterases before they reach the systemic circulation to the same active metabolite, monomethyl fumarate, upon oral administration. The PK comparability of diroximel fumarate to dimethyl fumarate through the analysis of monomethyl fumarate exposure has been demonstrated (see section 5.2), thus efficacy profiles are expected to be similar.

Clinical studies with dimethyl fumarate

Two, 2-year, randomised, double-blind, placebo-controlled studies (DEFINE with 1,234 patients and CONFIRM with 1,417 patients) of patients with RRMS were performed. Patients with progressive forms of MS were not included in these studies.

Efficacy (see table below) and safety were demonstrated in patients 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 CONFIRM contained a rater-blinded (i.e. study physician/ investigator assessing the response to study treatment was blinded) reference comparator of glatiramer acetate.

In DEFINE, 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 CONFIRM, 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, patients treated with dimethyl fumarate had a clinically meaningful and statistically significant reduction on the primary endpoint in study DEFINE, proportion of patients

relapsed at 2 years; and the primary endpoint in study CONFIRM, annualised relapse rate (ARR) at 2 years.

The ARR for glatiramer acetate and placebo was 0.286 and 0.401 respectively in study CONFIRM, corresponding to a reduction of 29% (p=0.013).

	DEFINE		**CONFIRM**		
	Placebo	**dimethyl fumarate 240 mg twice a day**	**Placebo**	**dimethyl fumarate 240 mg twice a day**	**Glatiramer acetate**
Clinical Endpoints[a]					
No. patients	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. patients	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; [b]MRI analysis used MRI cohort
*P-value < 0.05; **P-value < 0.01; ***P-value < 0.0001; #not statistically significant

An open non-controlled 8-year extension study (ENDORSE) enrolled 1,736 eligible RRMS patients from the pivotal studies (DEFINE and CONFIRM). The primary objective of the study was to assess the long-term safety of dimethyl fumarate in patients with RRMS. Of the 1,736 patients, approximately half (909, 52%) were treated for 6 years or longer. 501 patients were continuously treated with dimethyl fumarate 240 mg twice daily across all 3 studies and 249 patients who were previously treated with placebo in studies DEFINE and CONFIRM received treatment 240 mg twice daily in study ENDORSE. Patients who received treatment twice daily continuously were treated for up to 12 years.

During study ENDORSE, more than half of all patients treated with dimethyl fumarate 240 mg twice daily did not have a relapse. For patients continuously treated twice daily across all 3 studies, the adjusted ARR was 0.187 (95% CI: 0.156, 0.224) in studies DEFINE and CONFIRM and 0.141 (95% CI: 0.119, 0.167) in study ENDORSE. For patients previously treated with placebo, the adjusted ARR decreased from 0.330 (95% CI: 0.266, 0.408) in studies DEFINE and CONFIRM to 0.149 (95% CI: 0.116, 0.190) in study ENDORSE.

In study ENDORSE, the majority of patients (> 75%) did not have confirmed disability progression (measured as 6-month sustained disability progression). Pooled results from the three studies demonstrated dimethyl fumarate treated patients had consistent and low rates of confirmed disability progression with slight increase in mean EDSS scores across ENDORSE. MRI assessments (up to year 6, including 752 patients who had previously been included in the MRI cohort of studies DEFINE and CONFIRM showed that the majority of patients (approximately 90%) had no Gd-enhancing lesions. Over the 6 years, the annual adjusted mean number of new or newly enlarging T2 and new T1 lesions remained low.

Efficacy in patients with high disease activity:
In Studies DEFINE and CONFIRM, 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).

Clinical studies with Vumerity

The gastrointestinal tolerability of diroximel fumarate was evaluated in a randomised, multi-centre, phase 3 study (EVOLVE-MS-2) in 504 adult patients with RRMS. The study included a 5-week, double-blind treatment period with two treatment arms. Patients had a 1-week titration period and were randomised (1:1) to receive diroximel fumarate 462 mg twice daily (n=253) or dimethyl fumarate 240 mg twice daily (n=251). Patients had the following median baseline characteristics: age 44 years, disease duration 6.0 years and EDSS score 2.5. In this study, GI tolerability was investigated using the Individual GI Symptom and Impact Scale (IGISIS), which evaluated the incidence, intensity, onset, duration, and functional impact of five individual GI symptoms: nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhoea.

Overall gastrointestinal adverse reactions were observed in 34.8% of diroximel fumarate-treated patients and in 49.0% of dimethyl fumarate-treated patients. Treatment discontinuations were in total 1.6% and 6.0%, for diroximel fumarate and dimethyl fumarate, respectively. The discontinuations for gastrointestinal tolerability reasons were 0.8% and 4.8%, for diroximel fumarate and dimethyl fumarate, respectively. Treatment-emergent gastrointestinal adverse reactions of ≥ 5% for diroximel fumarate and dimethyl fumarate, respectively, were diarrhoea (15.4% and 22.3%), nausea (14.6% and 20.7%), upper abdominal pain (6.7% and 15.5%), abdominal pain (6.3% and 9.6%), lower abdominal pain (5.9% and 6.8%), and vomiting (3.6% and 8.8%).

Paediatric population

The efficacy of Vumerity in paediatric patients has not been established.

The European Medicines Agency has deferred the obligation to submit the results of studies with Vumerity in one or more subsets of the paediatric population in the treatment of MS (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Orally administered diroximel fumarate undergoes rapid presystemic hydrolysis by esterases and is primarily converted to the active metabolite, monomethyl fumarate, and the major inactive metabolite HES. Diroximel fumarate is not quantifiable in plasma following oral administration. Therefore, all pharmacokinetic analyses related to diroximel fumarate were performed with plasma monomethyl fumarate concentrations. Pharmacokinetic data were obtained from 10 clinical studies with healthy volunteers, 2 studies with MS patients and population PK analyses. Pharmacokinetic assessment has demonstrated that the exposure of monomethyl fumarate after oral administration of 462 mg diroximel fumarate and 240 mg dimethyl fumarate in adults is bioequivalent; therefore, diroximel fumarate is expected to provide a similar overall efficacy and safety profile to dimethyl fumarate.

Absorption

The median T_{max} of monomethyl fumarate is 2.5 to 3 hours. The peak plasma concentration (C_{max}) and overall exposure (AUC) increased dose proportionally in the dose range studied (49 mg to 980 mg). Following administration of diroximel fumarate 462 mg twice a day in MS patients in EVOLVE-MS-1, the mean C_{max} of monomethyl fumarate was 2.11 mg/L. The mean AUC_{last} after a morning dose was 4.15 mg.h/L. The mean steady state daily AUC (AUC_{ss}) of monomethyl fumarate was estimated to be 8.32 mg.h/L in MS patients.

Co-administration of diroximel fumarate with a high-fat, high-calorie meal did not affect the AUC of monomethyl fumarate but resulted in an approximately 44% reduction in C_{max} compared to fasted state. The monomethyl fumarate C_{max} with low-fat and medium-fat meals was reduced by approximately 12% and 25%, respectively.

Food does not have a clinically significant effect on exposure of monomethyl fumarate. Therefore, Vumerity may be taken with or without food (see section 4.2).

Distribution

The apparent volume of distribution (V_d) for monomethyl fumarate is between 72 L and 83 L in healthy subjects after administration of diroximel fumarate. Human plasma protein binding of monomethyl fumarate was less than 25% and was not concentration dependent.

Biotransformation

In humans, diroximel fumarate is extensively metabolised by esterases, which are ubiquitous in the gastrointestinal tract, blood, and tissues, before it reaches the systemic circulation. Esterase metabolism of diroximel fumarate produces predominantly 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 resulting metabolites of monomethyl fumarate in plasma.

Elimination

Monomethyl fumarate is mainly eliminated as carbon dioxide in the 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 diroximel fumarate. In a study with dimethyl fumarate, exhalation of CO_2 was determined to be the primary route of elimination accounting for approximately 60% of the dose. Renal and faecal

elimination are secondary routes of elimination, accounting for 15.5% and 0.9% of the dose, respectively.

HES is eliminated from plasma with a $t_{1/2}$ of 10.7 hours to 14.8 hours. HES is mainly eliminated in urine.

Linearity

Monomethyl fumarate exposure increases in an approximately dose proportional manner with single and multiple doses in the 49 to 980 mg dose range studied.

Pharmacokinetics in special patient groups

Body weight is the main covariate with monomethyl fumarate exposure increasing in C_{max} and AUC in participants with lower body weight after administration of diroximel fumarate. No effect was seen on safety and efficacy measures evaluated in the clinical studies. Therefore, no dose adjustments based on body weight are required.

Gender and age did not have a statistically significant impact on C_{max} and AUC of diroximel fumarate. The pharmacokinetics in patients aged 65 and over has not been studied.

Paediatric population

The pharmacokinetic profile of monomethyl fumarate after administration of diroximel fumarate has not been studied. The pharmacokinetic parameters of monomethyl fumarate after administration of diroximel fumarate are correlated to body weight. Therefore, it is anticipated that the same dose leads to a higher exposure in paediatric patients with lower body weight compared to adults. 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 dimethyl fumarate in these adolescent patients was similar with that previously observed in adult patients.

Race and ethnicity

Race and ethnicity have no effect on the pharmacokinetic profile of monomethyl fumarate or HES after administration of diroximel fumarate.

Renal impairment

In a study investigating the effect of renal impairment on the pharmacokinetic profile of diroximel fumarate, participants with mild (eGFR 60-89 mL/min/1.73cm^3), moderate renal impairment (eGFR 30-59 mL/min/1.73cm^3) or severe renal impairment (eGFR < 30 mL/min/1.73cm^3) had no clinically relevant changes in MMF exposure. However, HES exposure increased by 1.3-, 1.8-, and 2.7-fold with mild, moderate, and severe renal impairment, respectively (see section 4.8). There are no data available on long-term use of diroximel fumarate in patients with moderate or severe renal impairment (see sections 4.2 and 4.4).

Hepatic impairment

As diroximel 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 (see section 4.2 and 4.4).

5.3 Preclinical safety data

Toxicology

Kidney toxicity in rats and monkeys included tubular degeneration/necrosis with regeneration, tubular hypertrophy and/or interstitial fibrosis, increased kidney weights, and changes in clinical pathology parameters (urine volume, specific gravity, and biomarkers of kidney injury). In chronic toxicology studies, adverse renal findings occurred at monomethyl fumarate exposure that equalled the AUC at the maximum recommended human dose (MRHD) of diroximel fumarate.

Gastrointestinal toxicity in mice and rats consisted of mucosal hyperplasia and hyperkeratosis in the non-glandular stomach (forestomach) and duodenum. In monkeys, the poor gastrointestinal tolerability was characterised by dose-dependent emesis/vomitus, stomach irritation, haemorrhage and inflammation as well as diarrhoea. These findings developed at monomethyl fumarate exposure at least 2× the AUC at the MRHD of diroximel fumarate.

Cardiac inflammation and necrosis was seen in three male rats in the 91-day toxicity study at monomethyl fumarate exposure that was 4× the AUC at the MRHD of diroximel fumarate. These cardiac findings were also detected in other toxicity studies in rats including untreated controls, but not in monkeys. These cardiac inflammations therefore likely represent the exacerbation of common background lesions in rats without human relevance.

Partially-reversible physeal dysplasia of proximal and distal femur and proximal tibia was seen in monkeys in the 91-day toxicity study at monomethyl fumarate exposure that was 15× the AUC at the MRHD of diroximel fumarate. Bone toxicity might be related to the pre-pupertal age of the monkeys, because bone development was also impaired in juvenile rats (see below), but not affected at lower doses in the chronic monkey study or in mature adult rats. The bone findings are of limited relevance for adult patients at the therapeutic dose.

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 wild type littermates of *ras*H2 mice. These findings occurred at monomethyl fumarate exposure that was 15× the AUC at the MRHD of diroximel fumarate, indicating limited human relevance at the therapeutic dose.

Genotoxicity

In vitro and *in vivo* studies with diroximel fumarate did not provide evidence for a clinically relevant genotoxic potential.

Carcinogenesis

Diroximel fumarate was tested in a transgenic bioassay in transgenic *ras*H2 mice and a 2 year bioassay in rats. Diroximel fumarate was not carcinogenic in transgenic mice and in female rats, but increased the incidence of testicular Leydig cell adenomas at 150 mg/kg/day in male rats (monomethyl fumarate exposure was approximately 2× higher than the AUC at the MRHD). The relevance of these findings to human risk is unknown.

Reproduction and developmental toxicity

Diroximel fumarate did not impair male or female fertility in rats at monomethyl fumarate exposure that was approximately 7× the AUC at the MRHD of diroximel fumarate.

In rats administered diroximel fumarate orally during the period of organogenesis at doses of 40, 100 and 400 mg/kg/day lower fetal body weights and fetal skeletal ossification variations were observed at

a maternally toxic diroximel fumarate dose of 400 mg/kg/day. The exposure at the NOAEL was approximately 2× the AUC of monomethyl fumarate at the MRHD of diroximel fumarate.

In rabbits administered diroximel fumarate orally throughout organogenesis at doses of 50, 150 and 350 mg/kg/day, increases in skeletal malformations (vertebral centra anomaly, severely malaligned sternebra[e] and vertebral anomaly with associated rib anomaly) were observed at ≥ 150 mg/kg/day. At 350 mg/kg/day, increases in skeletal variations, abortions, higher post-implantation loss and corresponding decreases in fetal viability also occurred, possibly associated with maternal toxicity . The exposure at the NOAEL was approximately 2× the AUC of monomethyl fumarate at the MRHD of diroximel fumarate. The relevance of the skeletal malformations for humans is currently unknown.

In a pre- and post-natal development study in pregnant rats administered diroximel fumarate at oral doses of 40, 100, or 400 mg/kg/day during gestation through delivery and lactation reduced maternal body weight/weight gains and food consumption associated with reduced pup birth weights and body weight/weight gains were observed. The exposure at the NOAEL was approximately 3× the AUC of monomethyl fumarate at the MRHD of diroximel fumarate.

Toxicity in juvenile animals

In a juvenile rat toxicity study, diroximel fumarate was administered orally from postnatal day (PND) 25 through PND 63, equivalent to approximately 2-3 years old through to puberty in humans. In addition to the target organ toxicities in the kidney and non-glandular stomach, adverse effects in the bone were observed including decreased femur size, mass and density and changes in bone geometry. A relation of the bone effects to lower body weight is possible, but the involvement of a direct effect cannot be excluded. The exposure at the NOAEL was approximately 1.4× the AUC of monomethyl fumarate at the MRHD for adult patients of diroximel fumarate. The bone findings are of limited relevance for adult patients. The relevance for paediatric patients is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Methacrylic acid-ethyl acrylate copolymer (1: 1) type A
Crospovidone type A
Cellulose, microcrystalline
Silica, colloidal anhydrous
Triethyl citrate
Talc
Magnesium stearate

Capsule shell

Hypromellose
Titanium dioxide (E171)
Potassium chloride
Carrageenan

Capsule print (black ink)

Shellac
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

32 months

6.4 Special precautions for storage

Store below 25°C.

Store in the original bottle in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottle with a polypropylene child-resistant closure and a silica gel desiccant.
Pack size:
Packs of 120 (1 bottle) or 360 (3 bottles) gastro-resistant hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1585/001
EU/1/21/1585/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 November 2021

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Alkermes Pharma Ireland Limited
Connaught House
1 Burlington Road
Dublin 4
Ireland
D04 C5Y6

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vumerity 231 mg gastro-resistant hard capsules
diroximel fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 231 mg of diroximel fumarate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

120 gastro-resistant hard capsules
360 gastro-resistant hard capsules (3x120)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Do not crush or chew.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Store in the original bottle in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1585/001 120 gastro-resistant hard capsules
EU/1/21/1585/002 360 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vumerity

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Vumerity 231 mg gastro-resistant hard capsules
diroximel fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 231 mg of diroximel fumarate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

120 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Do not crush or chew.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
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EU/1/21/1585/002 360 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Vumerity 231 mg gastro-resistant hard capsules
diroximel fumarate

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

What is in this leaflet

1. What Vumerity is and what it is used for

What Vumerity is

Vumerity contains the active substance diroximel fumarate.

What Vumerity is used for

Vumerity is used to treat relapsing-remitting multiple sclerosis (MS) in adult patients.
MS is a long-term condition in which the immune system (the body's natural defences) malfunctions and attacks parts of the central nervous system (the brain, spinal cord and the optic nerve of the eye) causing inflammation that damages the nerves and the insulation around them. Relapsing-remitting MS is characterised by repeated attacks (relapses) on the nervous system. Symptoms vary from patient to patient, but typically include walking difficulties, feeling off balance and visual difficulties (e.g. blurred or double vision). These symptoms may disappear completely when the relapse is over, but some problems may remain.

How Vumerity works

The medicine is thought to work by increasing the action of a protein called 'Nrf2' which regulates certain genes that produce 'antioxidants' involved in protecting cells from damage. This helps control the activity of the immune system and reduce damage to the brain and spinal cord.

2. What you need to know before you take Vumerity

Do not take Vumerity

- **if you are allergic to diroximel fumarate, related substances (called fumarates or fumaric acid esters)** or any of the other ingredients of this medicine (listed in section 6).
- **if you are suspected to suffer from a rare brain infection called progressive multifocal leukoencephalopathy (PML) or if PML has been confirmed.**

Warnings and precautions

Vumerity may affect your **white blood cell counts**, your **kidneys** and **liver**. Before you start Vumerity, your doctor will do a blood test to count your white blood cells and will check that your kidneys and liver are working properly. Your doctor will test these periodically during treatment. If your white blood cells decrease during treatment, your doctor may consider additional tests or stop your treatment.

If you believe your MS is getting worse (e.g. weakness or visual changes) or if you notice any new symptoms, talk to your doctor straight away because these may be the symptoms of a rare brain infection called progressive multifocal leukoencephalopathy (PML). PML is a serious condition that may lead to severe disability or death. Read the information about 'PML and lower lymphocyte counts' in section 4 of this leaflet.

Talk to your doctor before taking Vumerity if you have:
- a serious **infection** (such as pneumonia)
- severe **kidney** disease
- severe **liver** disease
- a disease of the **stomach** or **bowel**

Flushing (reddening of the face and body) is a common side effect. Serious flushing with additional symptoms can be a sign of a severe allergic reaction and has been seen in a small number of patients – see 'Severe allergic reactions' in section 4 of this leaflet. Talk to your doctor if flushing is causing you problems, as your doctor may be able to give you medicine to treat this.

Vumerity can cause a serious allergic reaction known as a hypersensitivity reaction. You need to know about all of the important signs and symptoms to look out for while you are taking Vumerity. Read the information about 'Severe allergic reactions' in section 4 of this leaflet.

Shingles (*herpes zoster*) may occur with Vumerity treatment. In some cases, serious complications have occurred. **You should inform your doctor** immediately if you suspect you have any symptoms of shingles. These are listed in section 4 of this leaflet.

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

Children and adolescents

Do not give this medicine to children and adolescents because there is limited experience to know how safe and effective Vumerity is in this population.

Other medicines and Vumerity

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
In particular:
- medicines that contain **fumaric acid esters** (fumarates)
- **medicines that affect the body's immune system** including **chemotherapy**, **immunosuppressants** or **other medicines used to treat MS**
- **medicines that affect the kidneys including** some **antibiotics** (such as *aminoglycosides* used to treat infections), "**water tablets**" (*diuretics*), **certain types of painkillers** (such as ibuprofen and other similar anti-inflammatories and medicines purchased without a doctor's prescription) and medicines that contain **lithium**

- Taking Vumerity with certain types of vaccines (*live vaccines*) may cause you to get an infection and should, therefore, be avoided. Your doctor will advise whether other types of vaccines (non-live vaccines) should be given.

Pregnancy and breast-feeding

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

Pregnancy

Do not use Vumerity if you are pregnant unless you have discussed this with your doctor. This is because Vumerity could harm your unborn baby. If you are able to get pregnant, you should use reliable contraception.

Breast-feeding

It is not known whether diroximel fumarate or its metabolites pass into breast milk. Your doctor will help you decide whether you should stop breast-feeding or stop using Vumerity. This involves balancing the benefit of breast-feeding for your child, and the benefit of therapy for you.

Driving and using machines

Vumerity is not expected to affect your ability to drive and use machines.

3. How to take Vumerity

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

Starting dose

The recommended starting dose is 231 mg (one capsule) twice a day.
Take this starting dose for the first 7 days, then take the maintenance dose.

Maintenance dose

The recommended maintenance dose is 462 mg (two capsules) twice a day.

Vumerity is for oral use.

Swallow each capsule whole, with some water. Do not crush or chew or sprinkle the capsule contents on food as this may increase some side effects.

You can take Vumerity with a meal or on an empty stomach. If you have side effects such as flushing or stomach problems, taking it with food may reduce these symptoms.

If you take more Vumerity than you should

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

If you forget to take Vumerity

Do not take a double dose to make up for a forgotten dose.

If there are still at least 4 hours until your next planned dose, you can take the missed dose. Otherwise skip the missed dose and take your next planned dose at the normal time.

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

4. Possible side effects

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

Serious effects

PML and lower lymphocyte counts

The frequency of PML cannot be estimated from the available data (not known).

Vumerity may lower lymphocyte counts (a type of white blood cell). Having a low white blood cell count can increase your risk of infection, including the risk of a rare brain infection called progressive multifocal leukoencephalopathy (PML). PML may lead to severe disability or death. PML has occurred after 1 to 5 years of treatment with the related medicine dimethyl fumarate and so your physician should continue to monitor your white blood cells throughout your treatment, and you should remain observant of any potential symptoms of PML as described below. The risk of PML may be higher if you have previously taken a medicine that suppresses your body's immune system.

The symptoms of PML may be similar to an MS relapse. Symptoms may include new or worsening weakness on one side of the body, clumsiness, changes in vision, thinking, or memory, or confusion or personality changes, or speech and communication difficulties lasting for more than several days. Therefore, if you believe your MS is getting worse or if you notice any new symptoms while you are on Vumerity treatment, it is very important that you speak to your doctor as soon as possible. Also speak with your partner or caregivers and tell them about your treatment. Symptoms might develop that you do not notice yourself.

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

Severe allergic reactions

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

Flushing is a very common side effect. However, should flushing be accompanied by a red rash or hives **and** you get any of these symptoms:

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

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

→ Stop taking Vumerity and call a doctor straight away

Other side effects

Very common (may affect more than 1 in 10 people)
- reddening of the face or body feeling warm, hot, burning or itchy *(flushing)*
- loose stools *(diarrhoea)*
- feeling sick *(nausea)*
- stomach pain or stomach cramps

Side effects which may show up in your blood or urine tests
- substances called ketones, which are naturally produced in the body, very commonly show up in urine tests while taking Vumerity.
- low levels of white blood cells (*lymphopenia, leukopenia*) in the blood. Reduced white blood cells could mean your body is less able to fight an infection. If you have a serious infection (such as pneumonia), talk to your doctor immediately

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

Common (may affect up to 1 in 10 people)
- inflammation of the lining of the intestines (*gastroenteritis*)
- being sick *(vomiting)*
- indigestion (*dyspepsia*)
- inflammation of the lining of the stomach (*gastritis*)
- digestive system problems *(gastrointestinal disorder)*
- burning sensation
- hot flush, feeling hot
- itchy skin (*pruritus*)
- rash
- pink or red blotches on the skin (*erythema*)
- hair loss (*alopecia*)

Side effects which may show up in your blood or urine tests
- proteins (*albumin*) in urine (*proteinuria*)
- increase in levels of liver enzymes (*ALT, AST*) in the blood

Uncommon (may affect up to 1 in 100 people)
- Allergic reactions (*hypersensitivity*)
- reduction in blood platelets

Not known (frequency cannot be estimated from the available data)
- liver injury due to medication and increase in levels of liver enzymes measured in blood tests (*ALT or AST in combination with bilirubin*)
- shingles (*herpes zoster*) with symptoms such as blisters, burning, itching or pain of the skin, typically on one side of the upper body or the face, and other symptoms, like fever and weakness in the early stages of infection, followed by numbness, itching or red patches with severe pain
- runny nose (*rhinorrhoea*)

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

5. How to store Vumerity

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

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

Store below 25ºC.
Store in the original bottle in order to protect from moisture.

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

6. Contents of the pack and other information

What Vumerity contains

The active substance is diroximel fumarate.

Each capsule contains 231 mg of diroximel fumarate.

The other ingredients are: capsule contents: methacrylic acid-ethyl acrylate copolymer (1:1) type A; crospovidone type A; cellulose, microcrystalline; silica, colloidal anhydrous; triethyl citrate; talc; magnesium stearate; capsule shell: hypromellose; titanium dioxide (E171); potassium chloride; carrageenan; capsule print: black iron oxide (E172), shellac, potassium hydroxide.

What Vumerity looks like and contents of the pack

Vumerity 231 mg gastro-resistant hard capsules are white and printed with 'DRF 231 mg' in black ink.
Vumerity is available in packs containing 120 or 360 (3x120) capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Manufacturer

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Other sources of information

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