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CONSENSUS MEETING REPORT

Clinical use of dimethyl fumarate in moderate-to-severe plaque-type psoriasis: a European expert consensus

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Abstract Fumaric acid esters (FAEs) are a group of small molecules that were first investigated for the treatment of psoriasis in 1959. The first fumarate-based drug – Fumaderm® – was approved in Germany in 1994 for severe psoriasis and then in 2008, the label was expanded to include moderate psoriasis. Fumaderm is a combination of different FAEs: dimethyl fumarate (DMF), which is regarded as the main active component, plus calcium, magnesium and zinc salts of monoethyl fumarate (MEF). FAEs are the most frequently used first-line systemic psoriasis treatment in Germany, with an overall treatment experience comprising more than 220 000 patient-years. FAEs have demonstrated good, sustained clinical efficacy with an acceptable safety profile for the long-term treatment of patients with moderate-to-severe psoriasis. Indeed, the European S3-Guideline on the systemic treatment of *Psoriasis vulgaris* recommends FAEs for induction and long-term treatment. Until recently, FAEs were only licensed (for the psoriasis indication) in Germany, but were imported to many other European countries, such as The Netherlands, UK, Ireland, Austria and Italy, for the treatment of psoriasis. In 2017, the European Medicines Agency (EMA) approved Skilarence®, a new oral formulation of DMF, for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis in need of systemic therapy. Skilarence only contains DMF and is the first FAE for the treatment of psoriasis that has been approved by the EMA. This approval has given rise to a new oral treatment option for patients with moderate-to-severe plaque psoriasis across Europe. Here, we report the results of an expert meeting which was convened to deliver clinician-agreed consensus and real-world guidance on the clinical use of DMF in moderate-to-severe chronic plaque psoriasis. Guidance on appropriate patient selection, DMF dosage considerations, monitoring and side-effect management is offered based upon available evidence and collective real-world clinical experience.
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Conflicts of interest

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Introduction

Psoriasis is a chronic, inflammatory, immune-mediated disease with an estimated prevalence of approximately 2–4% in Europe.[1,2] Chronic plaque psoriasis is the most common type of psoriasis affecting around 90% of all patients[3] and up to a third of patients have moderate-to-severe disease.[4,5] Psoriasis is associated with an increased risk of early mortality, an increased prevalence of co-morbidity such as psoriatic arthritis, metabolic syndrome, and can have significant psychosocial impact which adversely affects patients' quality of life.[6]

A greater understanding of the pathogenesis of psoriasis has led to increased therapeutic options. The current treatments for psoriasis include topical therapies, phototherapy, PUVA (psoralen and ultraviolet A), systemic non-biologic therapies including conventional and newer oral agents, and biological therapies. For mild psoriasis, topical therapies are most commonly used with the addition of phototherapy in cases of insufficient response or acute episodes. In the presence of moderate-to-severe psoriasis, the initiation of systemic therapy is recommended.

There are various tools to assess the severity and impact of psoriasis. The Psoriasis Area and Severity Index (PASI) is an established parameter to measure the severity of skin symptoms and is the most commonly used tool; additional tools include: body surface area (BSA) and the Physician Global Assessment (PGA) (alternatively designated as the Investigator's Global Assessment or IGA).[7–9] Patient quality of life can be assessed by questionnaires including the Dermatology Life Quality Index (DLQI) and the Short Form (SF-36) Health Survey.[10,11] Despite the various tools, there is no definitively accepted definition of what encompasses mild, moderate or severe psoriasis. Moderate-to-severe disease is defined as a PASI >10 in the European S3-Guideline and the concept of the 'rule of tens' (BSA >10 or PASI >10 or DLQI >10) can be applied in the clinical setting for defining severe psoriasis.[12,13] From clinical experience, some patients with PASI <10, DLQI <10 and BSA <10 can be candidates for systemic treatment because therapy selection tries to capture a host of factors when making a treatment decision; it is beyond a simple severity assessment tool.

Unmet treatment needs still remain despite the wide range of therapeutic options, and many patients with psoriasis are not receiving treatment or are undertreated.[14] Data from a survey of 5604 patients with psoriatic disease from 2003 to 2011 showed that topical therapy was the sole method of treatment for a significant proportion of patients who were treated.[14,15] Despite systemic therapy being recommended for moderate-to-severe psoriasis, the survey revealed that approximately 30% of patients with moderate psoriasis and approximately 20% of patients with severe psoriasis were only receiving topical treatment. In addition, more than half of the patients with psoriasis were dissatisfied with their treatment. Many patients are not receiving the optimal therapy that is required to not only treat skin symptoms but also address the underlying inflammation and associated co-morbidity (cardiovascular disease, psoriatic arthritis, metabolic syndrome).[6,16]

Fumaric acid esters (FAEs) are a group of small molecules that were first investigated for the treatment of psoriasis in 1959.[17] The first fumarate-based drug was approved in

Germany in 1994 (Fumaderm Initial, Fumaderm; Fumapharm/Biogen Idec). Fumaderm was initially licensed for the treatment of severe psoriasis in adult patients and afterwards, in 2008, the label was expanded to include patients with moderate psoriasis. Fumaderm is a combination of different FAEs: dimethyl fumarate (DMF) plus calcium, magnesium and zinc salts of monoethyl fumarate (MEF).[18–20] DMF is considered to be the main active ingredient accounting for the clinical effects in psoriasis.[19] FAEs are the most frequently used systemic treatment in Germany with more than 220 000 patient-years of experience.[21] Until recently, FAEs were only licensed in Germany for the treatment of psoriasis but were imported to many other European countries.[19] In 2017, the European Medicines Agency (EMA) approved Skilarence®, a new oral formulation of DMF (Almirall S.A.), for the treatment of adults with moderate-to-severe chronic plaque psoriasis in need of systemic medical therapy.

Skilarence is the first FAE for the treatment of psoriasis that has been approved by the EMA. Skilarence contains DMF (which is considered to be the main active ingredient), at the same amount as in Fumaderm, but does not contain MEF salts. DMF is considered as a pro-drug for oral use to generate sufficient blood and tissue levels of monomethyl fumarate (MMF), the active *in vivo* metabolite.[19] The approximate t_{max} of MMF is 3.5 h in the fasting state and 9 h in the fed state.[19,22] DMF does not show any binding affinity to serum proteins, although MMF is approximately 50% bound.[19] Metabolism of MMF occurs through the tricarboxylic acid cycle, leading to excretion primarily through respiration, with no known involvement of the cytochrome P450 system.[23]

The anti-inflammatory and immunomodulating effects of MMF are not fully elucidated.[19] The main activity is considered to be immunomodulatory, inhibiting NF-κB translocation leading to reduced inflammatory cytokine production with induction of pro-apoptotic events, inhibition of keratinocyte proliferation, reduced expression of adhesion molecules, and diminished inflammatory infiltrate within psoriatic plaques.[19,24]

FAEs have demonstrated sustained clinical efficacy with an acceptable safety profile.[25] The European S3-Guideline on the systemic treatment of *Psoriasis vulgaris* recommends FAEs for induction treatment and long-term treatment of psoriasis.[13] Now, with the EMA approval of DMF, a new oral treatment option exists for adults with moderate-to-severe plaque psoriasis across Europe. Nevertheless, for many aspects of psoriasis treatment, there is no published evidence and expert consensus is needed to guide best clinical practice. Therefore, in the case of FAEs, here, we report the results of an expert meeting which was convened to deliver expert-agreed consensus and real-world guidance on the clinical use of DMF in moderate-to-severe chronic plaque psoriasis.

Methodology

The expert consensus panel brought together 10 dermatologists from across Europe with extensive clinical experience in managing patients with moderate-to-severe psoriasis and significant experience of using FAEs in clinical practice; furthermore, several of the panellists had experience in drawing up national and European-level clinical guidelines in psoriasis, including the 2015 update of the European S3-Guideline on the systemic treatment of psoriasis vulgaris.[13] Collectively, the panel represented 10 internationally-recognized centres for the treatment of psoriasis across eight European countries.

The objective of the meeting was to establish a consensus for the clinical use of DMF in moderate-to-severe chronic plaque psoriasis, with specific reference to dosing and side-effect management, based upon the available evidence and the experts' extensive clinical experience.

Initial consensus was reached in the roundtable of six experts, moderated by the first/lead author, with initial statements developed under the headings below, namely: patient profile and selection; dosage considerations; side-effects management. These initial statements were then refined with input from both the roundtable participants and the four other experts. Agreements and disagreements were discussed, and the reasons and evidence behind these statements were developed. Where there were a range of views or different views, these were expressed in the text developed around the statements; where consensus was reached, these were made part of the statements.

The expert panel consensus was drawn up with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument[26] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[27,28] to aid in the evaluation of the quality of evidence where available, identification of areas where expert consensus was needed to best guide clinical practice where no published evidence exists, and the strength of recommendations (based on the synthesis of high-quality evidence and expert clinical practice experience) to provide useful and practical guidance on the clinical use of DMF in moderate-to-severe plaque-type psoriasis for dermatological clinicians and clinics across Europe.

Patient profile and selection

The choice of systemic therapy should be individually considered in the context of each patient. Many patient-related factors have to be taken into account during therapeutic decision making, such as age and sex of the patient, co-morbidity and co-medication, plans to have children, disease dynamics and course, involvement of joints/psoriatic arthritis, and previous psoriasis treatments received. The individual patient's situation also needs to be considered such as occupation, ability to attend appointments, impairment of quality of life, as well as the manifestation of disease.

DMF is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients qualifying for systemic therapy. Fumarates should not primarily be used in erythrodermic psoriasis, non-stable, rapidly progressing plaque psoriasis, generalized pustular psoriasis or in patients with psoriatic arthritis.

DMF should be positioned among other non-biologic systemic treatments. In Germany and The Netherlands, FAEs are positioned as a first-line systemic treatment for moderate-to-severe psoriasis and are the most frequently prescribed systemic treatment for psoriasis, whereas in other European countries methotrexate (MTX) is mostly regarded as the standard first-line systemic treatment; for example, MTX is the most frequent first-line therapy in Ireland and is also first-line in Denmark. It was concluded by the panel that DMF should be considered a first-line treatment option in systemic-naïve patients with moderate-to-severe psoriasis. DMF may be used in patients who are candidates for methotrexate, cyclosporin and acitretin. FAEs can also be used in patients who have been previously treated with other systemic agents.[29] There is emerging evidence that DMF may even work in biologic non-responders; however, the priority should be use before the biologics.

According to the European S3-Guideline, moderate-to-severe disease is defined as a PASI >10.[13] In 2011, a European Consensus Programme defined treatment goals for moderate-to-severe psoriasis.[30] Moderate-to-severe disease was defined as: BSA >10 and DLQI >10 or PASI >10 and DLQI >10. Mild psoriasis was defined as: PASI ≤10 and BSA ≤10 and DLQI ≤10. The presence of certain psoriasis characteristics can, however, upgrade mild disease to moderate-to-severe. These include major involvement of visible areas, major involvement of the scalp, involvement of genitals, involvement of palms and/or soles, onycholysis or onychodystrophy of at least two fingernails, presence of itch leading to scratching and the presence of recalcitrant plaques. Although DMF is indicated for moderate-to-severe plaque psoriasis and indeed the majority of patients will fall into this category, in special clinical situations the European consented upgrade criteria can be applied and patients with mild disease (according to PASI) can be re-classified as moderate-to-severe. In the countries where fumarates have been available, many patients with mild-to-moderate psoriasis have been treated/are currently being treated with FAEs, if topical treatment was not effective or inappropriate.[25] Similarly, MTX is also used to treat patients not fulfilling the definition of moderate-to-severe psoriasis.

In terms of patient population, fumarates are equally effective in male and female patients, and young and elderly patients. Dose adjustment is not necessary in patients with mild-to-moderate renal impairment or in elderly patients. Although the use of DMF in the paediatric population is off-label, there are numerous case reports, case series and unpublished clinical experience to suggest that FAEs may be an effective treatment option for children and adolescents if a systemic therapy is indicated.[31–35] A German multicentre, retrospective study on the efficacy and safety of long-term use of FAEs in children and adolescents showed that FAEs were often used successfully in clinical practice as off-label therapy.[36] Trials of DMF in paediatric populations and for more moderate disease are ideally needed.

DMF is not recommended in women of child-bearing potential who are not using appropriate contraception. DMF should not be taken if patients are pregnant, breast-feeding or trying to become pregnant. Although in clinical practice, patients may become pregnant while on DMF, there are no published reports of this. Unlike other systemic treatments such as MTX, contraception for male patients under FAE treatment is not required.

There is no evidence of drug–drug interactions as FAEs are not metabolized by common pathways such as cytochrome P450-dependent mono-oxygenases.[19,25,37] Therefore, DMF can be used in patients with co-medication.[38] In this respect, DMF may be advantageous over other systemic treatments, such as MTX and cyclosporin, which have known interactions with several frequently used medications, such as non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs). Due to the scarcity of data, DMF should be used cautiously in combination with other systemic anti-psoriatic therapies such as MTX or cyclosporin and only in exceptional clinical circumstances.

Screening for hepatitis B/C, latent tuberculosis, or HIV-positivity is not mandatory with DMF. However, in cases of active hepatitis, tuberculosis, or HIV-positivity, an appropriate specialist should be contacted before treatment decisions are made. For patients with pre-existing infections of clinical relevance, the physician should decide if treatment with DMF should only be initiated once the infection has resolved. If a patient develops an infection during treatment with DMF, then suspension of treatment should be considered and the benefits and risks should be re-assessed prior to re-initiation of therapy. There are no published data/safety signals on treatment with fumarates in patients with a history of previous malignancies.

Lactose intolerance is not a contraindication to using DMF. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take Skilarence because the tablets contain lactose. DMF is contraindicated in patients with severe renal or hepatic impairment or with severe gastrointestinal disorders, such as duodenal ulcer or active severe inflammatory bowel disease (IBD). FAEs do not appear to improve or exacerbate IBD. They can, however, cause diarrhoea and their use in patients with known gastrointestinal disorders should be done in conjunction with a gastroenterologist.

Dosage considerations

It is important to set clear treatment expectations with patients in order to improve treatment adherence. FAEs are slow-acting drugs that often require several weeks to exert a meaningful clinical response. During this time, patients may experience the

well-known, initial side-effects of FAEs that are often experienced during treatment initiation/up-titration. To improve tolerability, it is recommended to begin treatment with a low initial dose of DMF with subsequent gradual increases over 9 weeks. Treatment with DMF does allow for flexible and individualized dosing according to patient clinical response and tolerability. Once a patient's individual maintenance dose has been achieved, DMF can offer a long-term treatment option with sustained efficacy and an acceptable safety profile.[39] FAEs have an excellent drug survival, with up 60% of patients remaining on treatment for 4 years.[40]

In order to enhance the clinical improvement and efficacy outcomes during the first weeks of therapy with FAEs, combined treatment with topical therapy or phototherapy is recommended. A multicentre, randomized, double-blind trial demonstrated that the combination of topical calcipotriol and FAEs was significantly more effective, leading to a quicker clinical response, than FAE monotherapy.[41] The combination of FAEs with phototherapy may also induce a faster therapeutic response during the induction phase.[42,43]

There are two available doses of DMF: 30 mg and 120 mg. The recommended dosing schedule can be followed using the 30 mg and 120 mg tablets until the maximum daily dose of 720 mg (3 × 2 tablets of DMF 120 mg) is reached, but individual dosing at different time points is possible.[37] The dosing schedule is as follows: Week 1, one 30 mg tablet daily; Week 2, two 30 mg tablets daily and Week 3, three 30 mg tablets daily. At Week 4, patients switch to 120 mg tablets, starting with one 120 mg tablet daily. After Week 4, an additional 120 mg tablet is added weekly until the maximum daily dose of 720 mg (3 × 2 tablets of DMF 120 mg) is reached. If a meaningful clinical response is achieved before the maximum dose is reached, no further increase of dose is necessary. Onset of a clinical response can be seen as early as Week 3, however, maximum efficacy is usually seen after 24 weeks.[37,44] Based upon the clinical experience with FAEs, in patients who do not show any degree of effect by Week 12, treatment with DMF should be discontinued. During the up-titration phase of treatment, it is encouraged that an early visit is scheduled (preferably one month after initiation of treatment) with the aim of increasing patient adherence by addressing any possible side-effects and/or dosing concerns the patient may have. For example, if a particular dose increase was not tolerated, it may be temporarily reduced to the last tolerated dose.

When a clinically meaningful improvement of the skin lesions has been achieved, consideration should be given to a gradual reduction of the daily dose of DMF, by removing one 120 mg pill per month, to achieve the maintenance dose required by the individual. Down-titration should be stopped when the patient reports that psoriasis is starting to re-appear (minimal relapse). The patient should then be up-titrated to the last efficacious dose. Most patients require between two and four 120 mg tablets a day (240 to 480 mg/day) during maintenance.

Patients should continue to take DMF while it continues to be efficacious and tolerated. A retrospective, single-centre study investigated the drug survival of FAEs in patients with psoriasis showed that FAEs have a favourable 4-year survival of 60%.[40] No treatment interruption (drug holidays) is necessary if the treatment is efficacious. If a patient has stopped taking the medication, the treating physician should ask how well DMF was tolerated prior to discontinuation. If there were no tolerability problems the patient can resume treatment at a higher dose. However, if the patient had some tolerability issues before, then the up-titration schedule should be followed again.

Side-effects management

FAEs have a well-characterized side-effect profile (Table 1) and most adverse events (AEs) experienced are mild and do not lead to discontinuation of treatment.[37,45] Side-effects are often exclusively experienced during the treatment initiation and up-titration phase and lessen over time once the patient becomes established on treatment. Because of this, it is important to align patients' expectations before starting treatment and explain that transient side-effects may be experienced during the first few weeks of treatment and discuss management strategies. It is important to communicate that after this transient period, when the individual maintenance dose is found, FAEs offer many advantages for the long-term treatment of psoriasis. An early visit, one month after treatment initiation, can be scheduled to discuss dosing and side-effect management.

Table 1 Frequency of adverse events with Skilarence

Very Common (≥1/10)	Lymphopenia; Leukopenia; Flushing; Diarrhoea; Abdominal distension; Abdominal pain; Nausea
Common (≥1/100 to <1/10)	Vomiting; Dyspepsia; Constipation; Abdominal discomfort; Decreased appetite; Flatulence; Hepatic enzymes increased; Headache; Paraesthesia; Eosinophilia; Leukocytosis; Erythema; Skin burning sensation; Pruritus; Fatigue; Feeling hot; Asthenia
Uncommon (≥1/1000 to <1/100)	Proteinuria; Serum creatinine increased; Dizziness

Gastrointestinal

Gastrointestinal side-effects such as diarrhoea, abdominal distension, abdominal pain, nausea, vomiting, dyspepsia, constipation, and flatulence, occur in up to 60% of patients on FAE treatment.[44] Despite the high rate of recurrence, gastrointestinal side-effects usually peak during the first weeks of treatment and improve over time; the general consensus of the expert panel was that between Weeks 3 and 6 the gastrointestinal side-effects

can become an issue, but by Weeks 8–9, symptoms should stabilize or improve.

In the majority of patients, gastrointestinal side-effects do not lead to treatment discontinuation, but dose adjustments may be required. However, in up to 20% of patients and depending on the patient, gastrointestinal side-effects may lead to drug discontinuation. Similar rates of gastrointestinal side-effects have been experienced across the countries where fumarates have been used and once a patient becomes established on FAEs, the development of gastrointestinal side-effects is uncommon.

No consistent dietary strategies such as taking medication in a fed vs. fasted state, or in the morning/evening, have been found to ameliorate the gastrointestinal symptoms. Prescribing other medications such as painkillers or anti-diarrhoea, to treat the gastrointestinal symptoms, is not recommended (though one of the members of the expert panel reported the use of the antispasmodic, mebeverine hydrochloride, as helpful).

Flushing

Skin flushing is experienced by approximately 30–50% of patients treated with FAEs; however, it rarely leads to patient discontinuation.[18] Patients should be made aware that they are likely to experience flushing symptoms (redness, warmth, tingling, itching) and should not be perceived by patients as an allergic reaction. Flushing symptoms are usually experienced in the first few weeks of taking DMF; however, flushing tends to lessen over time once the patient is established on treatment.[37]

Flushing usually begins shortly after taking FAEs and resolves within a few hours.[37] Flushing may also be influenced after alcohol intake or consumption of spicy food. If flush is severe, patients can take aspirin (500 mg) since pre-treatment with aspirin has been shown to reduce the incidence and intensity of flushing in patients taking DMF.[46,47] Regular intake of aspirin is not recommended, however. The patient can also be advised to take DMF in the evening to ameliorate possible side-effects.

Leukopenia, lymphopenia, and eosinophilia

Leukopenia, especially lymphopenia, may occur under treatment with FAEs. Lymphopenia is usually mild, mostly experienced during the initiation/dosage increase phase, and can be managed with dose adjustments in most cases.[18,45] Treatment discontinuation due to lymphopenia may be required in some cases.[18,45]

In the randomized, double-blind BRIDGE trial, lymphopenia was reported in 10% of patients in the Skilarence group and in 10.6% in the Fumaderm group.[44] In the retrospective FUTURE study on the long-term use of FAE in psoriasis, lymphopenia was reported in up to 41% of patients and leukopenia in 12% of patients after 24 months.[25] Severe lymphopenia is only reported in approximately 3% of patients being treated with FAEs.[48]

Before starting treatment with DMF, a complete blood count (including differential blood count and platelet count) should be performed and treatment should not be initiated if the leucocyte count is below 3.0×10^9/L or the lymphocyte count is below 1.0×10^9/L.

During treatment with DMF, monitoring visits should be scheduled every 3 months and a complete blood count with differential should be performed. If leucocytes fall below 3.0×10^9/L or the lymphocyte count falls below 1.0×10^9/L but is $\geq 0.7 \times 10^9$/L, blood monitoring should be performed monthly until the levels return to normal for two consecutive blood tests. At which point, monitoring can be performed again every 3 months. If the leucocyte count is below 3.0×10^9/L or the lymphocyte count falls below 0.7×10^9/L, the blood test must be repeated (after 1 month) and if the levels are confirmed to be below the thresholds, then treatment must be stopped immediately.

Patients developing lymphopenia should be monitored after stopping treatment until the lymphocyte count has returned to the normal range. If a patient develops lymphopenia and has to discontinue therapy, then the lymphopenia can be long lasting and recovery can be slow.[49]

Isolated cases of opportunistic infections, particularly of progressive multifocal leukoencephalopathy (PML), have been reported with FAE treatment and have been linked with prolonged, severe lymphopenia.[50–56] There have been 14 cases of PML reported in patients with psoriasis and five cases in patients with multiple sclerosis (MS) who were receiving FAE treatment.[54] The median duration of FAE therapy to PML diagnosis was 31 months (range 6–110) and in all cases lymphopenia was reported at diagnosis (average lymphocyte count: 538 cells/μL [normal range 1000–4000 cells/μL]). The average duration of lymphopenia to PML symptom onset was 29 months.

PML is a rare, but serious brain-demyelinating disease caused by the John Cunningham virus.[57] Considering that the overall treatment experience with Fumaderm comprises more than 220 000 patient-years of exposure, reports of PML are rare.[49] Severe lymphopenia is a risk factor for PML, therefore adherence to monitoring recommendations and lymphocyte cut-offs is essential to minimize risk.[49]

Laboratory thresholds for monitoring lymphocytes differ between Fumaderm and Skilarence, with the cut-off values being higher for Skilarence. Cut-off values for treatment discontinuation are a lymphocyte count of $<0.5 \times 10^9$/L for Fumaderm and $<0.7 \times 10^9$/L for Skilarence on two consecutive occasions. For Skilarence, if the lymphocyte count falls below 1.0×10^9/L but is $\geq 0.7 \times 10^9$/L, blood monitoring should be performed monthly until levels return to 1.0×10^9/L or higher for two consecutive blood tests. For Fumaderm, if lymphocytes fall below 0.7×10^9/L, the dose must be halved and if the lymphocyte count remains below 0.7×10^9/L after 4 weeks, treatment should be stopped.

With regards to eosinophil count, a transient increase may occur at the beginning of FAE treatment. However, eosinophilia is rare and self-limiting without dose adjustment.[37]

Box 1 Frequently asked questions (FAQ)

Are FAEs recommended in guidelines?
Yes. The European S3-Guideline recommends FAEs for induction treatment and long-term treatment of moderate-to-severe plaque psoriasis.[13]

Why is Fumaderm only available in Germany and no other European countries?
Fumaderm is not a DMF-only drug. Fumaderm contains DMF, calcium, magnesium and zinc salts of MEF. Due to this unique combination of salts and the empirical means of development, approval was never sought outside of Germany. However, FAEs are being used in the treatment of psoriasis in several other European countries through importing Fumaderm from Germany or by compounding FAEs.

Why are FAEs one of the most commonly prescribed treatments for psoriasis in Germany?
From a historical perspective, Fumaderm was initially licensed in Germany in 1994 and offered a new alternative to German dermatologists. For more than 20 years, Fumaderm has been the first-line, first-choice option for systemic therapy of psoriasis in Germany in patients without psoriatic arthritis.
FAEs have demonstrated good, sustained clinical efficacy with a favourable safety profile for the long-term treatment of patients with moderate-to-severe psoriasis.[25] FAEs have an excellent drug survival, with up 60% of patients remaining on treatment for 4 years.[40] In addition, FAEs offer an oral treatment option, which patients may find preferable to other treatments administered by injection, and flexible dosing which allows for individualization of dose. The extensive use of Fumaderm in Germany demonstrates that FAEs are an attractive treatment option for patients and physicians.

What special information do patients need before they start treatment with DMF?
The flexible-dosing schedule with DMF should be communicated. It should be explained that at the beginning of treatment a low dose of DMF is taken with subsequent gradual increases until the individual maintenance dose is achieved. In doing so, the treatment is tailored to suit each individual patient. It is also important to inform the patient that treatment can take some weeks to take effect and that there also may be initial side-effects (gastrointestinal, flushing) at the onset of therapy, which can be thought of as a temporary habituation phase, and while patients should be warned about the issues around lymphopenia, once patients become established on treatment, DMF has many long-term advantages.

What is the average number of tablets most patients need in the maintenance phase?
From clinical experience, most patients require between two and four 120 mg tablets of DMF per day (240 to 480 mg/day).

How long can patients continue to take FAEs?
The long-term safety profile of continuous FAE treatment is favourable and patients should stay on treatment while it continues to be efficacious and tolerated.[25,62] FAEs have an excellent drug survival, with up 60% of patients remaining on treatment for 4 years.[40]

Is development of PML associated with the use of FAEs?
Isolated cases of PML, have been reported with FAE treatment and have been predominantly linked with prolonged, severe lymphopenia.[54] Severe lymphopenia is a risk factor for PML, therefore adherence to monitoring recommendations and lymphocyte cut-offs is essential to minimize risk.

Laboratory thresholds for monitoring lymphocytes differ between Fumaderm and Skilarence, with the cut-off values being higher for Skilarence. Cut-off values for treatment discontinuation are a lymphocyte count of $<0.5 \times 10^9$/L for Fumaderm and $<0.7 \times 10^9$/L for Skilarence on two consecutive occasions. For Skilarence, if the lymphocyte count falls below 1.0×10^9/L but is $\geq 0.7 \times 10^9$/L, blood monitoring should be performed monthly until levels return to 1.0×10^9/L or higher for two consecutive blood tests. For Fumaderm, if lymphocytes fall below 0.7×10^9/L, the dose must be halved and if the lymphocyte count remains below 0.7×10^9/L after 4 weeks, treatment should be stopped.

Is DMF associated with an increased risk of infections or malignancies?
DMF is an anti-inflammatory and immunomodulatory agent and is not associated with increased risk of infections or malignancies (based on the short-term data currently available).[37] The rate of infections/infestations with Fumaderm is significantly lower

compared with other conventional psoriasis treatments (cyclosporin, methotrexate, retinoids). The rate of malignancies with Fumaderm is similar to other conventional psoriasis treatments.

Can DMF be used in patients who take co-medication because of their co-morbidity?
Yes. The majority of patients with psoriasis must take other medications due to the disease itself or because of associated co-morbidity (e.g., hypertension, Type 2 diabetes, depression).[63,64] Many psoriasis treatments require an adjustment in long-term medication due to drug interactions, cumulative toxicities or renal/hepatic decomposition mechanisms.[65] However, with DMF there is no evidence of drug–drug interactions and elimination mainly takes place by exhalation, therefore it can be used in patients with co-medications. No dose adjustment is required with DMF in elderly patients or in patients with mild-to-moderate hepatic or renal impairment.

Do fumarates need to be stopped due to surgical intervention?
No. There are no reports about a safety risk when continuing fumarates during surgical interventions.

Can patients receive vaccinations while being treated with DMF?
Vaccination during treatment with Skilarence has not been studied. A recent study with DMF in multiple sclerosis patients has reported that patients mounted an adequate immune response to inactivated vaccines.[66] There is no evidence of an impaired immune response to vaccination and in daily clinical practice, patients are not advised to suspend FAE treatment before vaccination with inactivated (as against live) vaccines.

Is DMF associated with contact dermatitis?
No. This is a historical association of when DMF was used as an anti-moulding agent in items, such as sofas and shoes, during haulage from China. The use of DMF in consumer products has now been banned by the EU.[67,68] No contact dermatitis has been observed with DMF tablets.

Is switching from one fumarate drug to another possible?
Yes. Patients can switch fumarate treatment from one day to another.

Renal function

Renal function (e.g., creatinine, blood urea nitrogen and urinalysis) should be checked prior to initiation of treatment and every 3 months thereafter.[37] Impairment of renal function may occur with FAE treatment; however, this is relatively infrequent.[58] Proteinuria may occur in up to 14% of patients but often does not result in dose reduction or treatment discontinuation. Proximal tubule dysfunction which leads to aminoaciduria is uncommon and reported in 4.7% of patients.[59] In the randomized, double-blind BRIDGE trial, proteinuria was reported in 4 patients (1.4%) in the Skilarence group and in 6 patients (2.1%) in the Fumaderm group.[44]

Urine dipsticks are widely used in clinical practice as an initial screening tool for proteinuria. While they may be advantageous at point of care, the preferred method to accurately quantify elevated protein is laboratory measurement of albumin-to-creatinine ratio (ACR). A population-based study which compared the urine dipstick with ACR reported that the sensitivity of the dipstick to detect ACR >30 mg/g was 44% with 96% positive/negative predictability.[60]

Proteinuria can be considered clinically significant at an ACR >30 mg/g. The 2012 KDIGO clinical practice guidelines recommended three categories of albuminuria to grade risk: normal to mildly increased (<30 mg/g); moderately increased (30–300 mg/g) and severely increased (>300 mg/g).[61] If significant proteinuria is detected, a first-morning urine analysis should be performed to exclude orthostatic proteinuria. Consideration should be given to dosage reduction or treatment discontinuation at an ACR >30 mg/g or protein-to-creatinine ratio (PCR) >200 mg/g. FAE dose reduction may also be required if proteinuria is detected along with low serum phosphate and/or low serum urate. If proteinuria is detected but serum creatinine levels are normal, both ACR and PCR should be measured in a spot urine sample. It is recommended that in cases of persistent/significant proteinuria, patients should be referred to a nephrologist.

Discussion

FAEs have long been used for the oral treatment of adults with moderate-to-severe plaque psoriasis.[44,62] FAEs are the most frequently used systemic treatment in Germany in patients with moderate-to-severe psoriasis and are increasingly being used in several European countries such as The Netherlands, UK, Ireland, Austria, and Italy.[21,69–74] Furthermore, European guidelines recommend the use of FAEs for the induction and long-term treatment of moderate-to-severe psoriasis.[13]

It is recommended to begin treatment with DMF with a low initial dose followed by subsequent gradual increases. Although there is a recommended dosing schedule, it is recommended by the panel to have flexible dosing according to the individual patient's needs and on average, most patients require between two and four 120 mg tablets of DMF a day.

There are several randomized clinical studies which have demonstrated the clinical efficacy and favourable safety profile of FAEs and an even greater number of observational studies which support the findings.[48] A recent Cochrane review assessed seven randomized controlled trials of FAEs in a total of 449 patients with psoriasis.[48] Due to the low number of trials and clinical heterogeneity, the efficacy data were not pooled for meta-analysis, but overall, mean PASI scores decreased by between 42 and 65% after 12–16 weeks of treatment. The review also included 37 observational studies with a total of 3457 patients, which supported the results from the clinical trials.

The Phase III, randomized, non-inferiority, BRIDGE study compared the efficacy and safety of Skilarence and Fumaderm vs. placebo in adult patients with moderate-to-severe chronic plaque psoriasis.[44] The co-primary efficacy endpoints were the percentage of patients achieving PASI 75 and a PGA score of 'clear' or 'almost clear' at Week 16. A total of 671 patients were randomized. At Week 16, PASI 75 was achieved by 37.5% of patients receiving Skilarence, 40.3% receiving Fumaderm and 15.3% receiving placebo. PGA scores of 'clear' or 'almost clear' were achieved by 33.0% of patients receiving Skilarence, 37.4% receiving Fumaderm and 13.0% receiving placebo. The BRIDGE

Table 2 Summary of expert consensus panel recommendations

Indication
• DMF is indicated for the treatment of moderate-to-severe plaque psoriasis in adults in need of systemic medicinal therapy
Guidelines
• The European S3-Guideline recommends FAEs for induction treatment and long-term treatment of moderate-to-severe plaque psoriasis
Patient profile and selection
• DMF can be positioned as a first-line treatment option in systemic therapy naïve patients with moderate-to-severe psoriasis
• The combination of DMF with topical therapy or phototherapy is recommended during the first few weeks of therapy
• Fumarates are equally effective in male and female patients, and young and elderly patients
• Dose adjustment is not necessary in patients with mild-to-moderate renal impairment or in elderly patients
• No evidence of drug–drug interactions, therefore DMF can be used in patients with co-medications
• Fumarates should not primarily be used in erythrodermic psoriasis, non-stable, rapidly progressing plaque psoriasis, generalized pustular psoriasis, or in patients with psoriatic arthritis
Dosage considerations
• It is recommended to begin treatment with a low initial dose of DMF with subsequent gradual increases over 9 weeks
• The recommended dosing schedule can be followed using 30 mg and 120 mg tablets until the maximum allowed daily dose of 720 mg is reached, but individual dosing at different time points is possible
• Treatment with DMF does allow for flexible and individualized dosing according to patient clinical response and tolerability
• Onset of a clinical response can be seen as early as Week 3; maximum efficacy is usually seen after 24 weeks
• It is important to set clear treatment expectations with patients and an early visit should be scheduled (ideally 1 month after initiation of treatment) to address any concerns the patient may have about dosing and/or side-effects
Side-effects management
• The long-term safety profile of continuous FAE treatment is favourable and patients should stay on treatment while it continues to be efficacious and tolerated
• FAEs have a well-characterized side-effect profile and most adverse events (AEs) experienced are mild and do not lead to treatment discontinuation
• Side-effects are often exclusively experienced during the treatment initiation and up-titration phase and lessen over time once the patient becomes established on treatment
• Patients' expectations should be managed before starting treatment with the explanation that transient side-effects may be experienced during the first few weeks of treatment and possible management strategies should be discussed
• Gastrointestinal disorders, followed by flushing are the most common AEs
• In the majority of patients, gastrointestinal side-effects do not lead to treatment discontinuation, but dose adjustments may be required. However, in up to 20% of patients and depending on the patient, gastrointestinal side-effects may lead to drug discontinuation
• Skin flushing is experienced by approximately 30–50% of patients treated with FAEs; however, it rarely leads to patient discontinuation
• Leukopenia, especially lymphopenia, may occur under treatment with FAEs. Lymphopenia is usually mild, mostly experienced during the initiation/dosage increase phase, and can be managed with dose adjustments in most cases
• It is essential to adhere to monitoring recommendations and laboratory thresholds
• During treatment, monitoring visits should be scheduled every 3 months for Skilarence and every 4 weeks for Fumaderm and a complete blood count with differential should be performed

study demonstrated that Skilarence was non-inferior to Fumaderm, with a similar safety profile.

The large retrospective, FUTURE study collected real-world data on the safety and efficacy FAEs in Germany with 984 patients who had either been treated continuously with FAEs for at least 24 months, or for 36 months with interruptions of no longer than 6 months.[25] Most patients had a diagnosis of chronic stable plaque psoriasis (87%). According to PGA scores at baseline, 30% of patients had moderate psoriasis, 40% had moderate-to-severe disease and 23% had severe psoriasis. The majority of patients (81%) had received FAEs as first-line systemic treatment. After 6 months of treatment, 67% of patients were reported to have markedly improved or clear disease, which increased to 78% of patients after 24 months, and 82% patients after 36 months. PASI values were available for 107 patients and subgroup analysis showed a mean reduction in PASI from baseline of 79%. The FUTURE study provides an overview of the real-world use of FAEs in everyday practice for the successful long-term treatment of patients.

Combination of FAEs with topical treatments or phototherapy may induce faster therapeutic responses during the induction phase.[42,43] More recently, there has been an interest in the combination of FAEs with biological therapies. A retrospective chart review in 6 specialized dermatological departments in Germany identified 17 cases of patients receiving FAEs combined with one other conventional systemic agent or biological therapy.[75] There has also been randomized exploratory study of 33 patients, which prospectively assessed the efficacy, safety and tolerability of the combination of etanercept with FAEs vs. etanercept monotherapy.[76]

The safety profile of FAEs is well characterized.[77] Adverse events during treatment with FAEs are reported in up to two-thirds of all patients but are mostly mild and do not lead to treatment discontinuation.[37,45] Side-effects, mainly comprising gastrointestinal disorders and flushing, are often experienced during the treatment initiation and up-titration phase and lessen over time once the patient becomes established on treatment. To improve gastrointestinal tolerability, it is recommended to gradually increase dose and if a particular dose increase is not tolerated, it can be temporarily reduced to the last tolerated dose. Other characteristic side-effects of FAEs include leukopenia and lymphopenia. Lymphopenia is usually mild and mostly experienced during the treatment initiation and up-titration phase. Lymphopenia can be managed with dose adjustments in most cases, though treatment discontinuation may be required in some cases.[18,45] While patients are on FAE treatment, it is important to adhere to monitoring recommendations and the recommended cut-off lymphocyte values to minimize the risk of opportunistic infections.

The long-term safety profile of continuous FAE treatment is favourable and patients should stay on treatment while it continues to be efficacious and tolerated.[25,62] FAEs are not associated with increased risk of infection or malignancy. FAEs can be used in patients with co-medication because there is no evidence of drug–drug interactions.[25,37] In this respect, DMF may be advantageous over other systemic treatments, such as methotrexate and cyclosporin, which have known interactions with common medications.[38,78] In addition, FAEs have an excellent drug survival, with up 60% of patients remaining on treatment for 4 years.[40]

This was an expert consensus to deliver real-world guidance on the clinical use of DMF in moderate-to-severe chronic plaque psoriasis. The consensus was developed to aid dermatologists in clinical practice and is based upon available evidence and collective real-world clinical experience. For clarity, a list of frequently asked questions (FAQs) has been developed based on the consensus discussion (Box 1), together with a summary of the key recommendations of the expert consensus panel (Table 2).

Conclusion

The favourable safety profile of FAEs together with their long-term efficacy provides a first-line therapeutic option to achieve sustained disease control for patients with moderate-to-severe plaque psoriasis, when psoriasis cannot be adequately controlled with topical treatments and phototherapy.

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Author contributions

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References

1 Boehncke WH, Schon MP. Psoriasis. *Lancet* 2015; **386**: 983–994.

2 Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013; **133**: 377–385.
3 Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007; **370**: 263–271.
4 Helmick CG, Lee-Han H, Hirsch SC, Baird TL, Bartlett CL. Prevalence of psoriasis among adults in the U.S.: 2003–2006 and 2009–2010 National Health and Nutrition Examination Surveys. *Am J Prev Med* 2014; **47**: 37–45.
5 Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003–2004. *J Am Acad Dermatol* 2009; **60**: 218–224.
6 Mrowietz U, Steinz K, Gerdes S. Psoriasis: to treat or to manage? *Exp Dermatol* 2014; **23**: 705–709.
7 Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. *Dermatologica* 1978; **157**: 238–244.
8 Langley RG, Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment. *J Am Acad Dermatol* 2004; **51**: 563–569.
9 Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point investigator's global assessment (IGA) scale: a modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatolog Treat* 2015; **26**: 23–31.
10 Finlay AY, Khan GK. Dermatology life quality index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–216.
11 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473–483.
12 Finlay AY. Current severe psoriasis and the rule of tens. *Br J Dermatol* 2005; **152**: 861–867.
13 Nast A, Gisondi P, Ormerod AD *et al.* European S3-Guidelines on the systemic treatment of psoriasis vulgaris—Update 2015—Short version—EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol* 2015; **29**: 2277–2294.
14 van de Kerkhof PC, Reich K, Kavanaugh A *et al.* Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the population-based multinational assessment of psoriasis and psoriatic arthritis survey. *J Eur Acad Dermatol Venereol* 2015; **29**: 2002–2010.
15 Augustin M, Reich K, Reich C *et al.* Quality of psoriasis care in Germany—results of the national study PsoHealth 2007. *J Dtsch Dermatol Ges* 2008; **6**: 640–645.
16 Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. *J Eur Acad Dermatol Venereol* 2012; **26**(Suppl. 2): 3–11.
17 Schweckendiek W. [Treatment of psoriasis vulgaris]. *Med Monatsschr* 1959; **13**: 103–104.
18 Mrowietz U, Altmeyer P, Bieber T, Rocken M, Schopf RE, Sterry W. Treatment of psoriasis with fumaric acid esters (Fumaderm). *J Dtsch Dermatol Ges* 2007; **5**: 716–717.
19 Mrowietz U, Morrison PJ, Suhrkamp I, Kumanova M, Clement B. The pharmacokinetics of fumaric acid esters reveal their in vivo effects. *Trends Pharmacol Sci* 2018; **39**: 1–12.
20 Rostami Yazdi M, Mrowietz U. Fumaric acid esters. *Clin Dermatol* 2008; **26**: 522–526.
21 Reich K, Mrowietz U, Radtke MA *et al.* Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. *Arch Dermatol Res* 2015; **307**: 875–883.
22 Litjens NH, Burggraaf J, van Strijen E *et al.* Pharmacokinetics of oral fumarates in healthy subjects. *Br J Clin Pharmacol* 2004; **58**: 429–432.
23 Hochadel MA. Mosby's Drug Reference for Health Professions, 5th edn. Elsevier Health Sciences, St. Louis, MO, 2016.
24 de Jong R, Bezemer AC, Zomerdijk TP, van de Pouw-Kraan T, Ottenhoff TH, Nibbering PH. Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate. *Eur J Immunol* 1996; **26**: 2067–2074.
25 Reich K, Thaci D, Mrowietz U, Kamps A, Neureither M, Luger T. Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis—a retrospective study (FUTURE). *J Dtsch Dermatol Ges* 2009; **7**: 603–611.
26 Brouwers MC, Kerkvliet K, Spithoff K. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016; **352**: i1152.
27 Andrews JC, Schunemann HJ, Oxman AD *et al.* GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013; **66**: 726–735.
28 Andrews J, Guyatt G, Oxman AD *et al.* GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013; **66**: 719–725.
29 Harries MJ, Chalmers RJ, Griffiths CE. Fumaric acid esters for severe psoriasis: a retrospective review of 58 cases. *Br J Dermatol* 2005; **153**: 549–551.
30 Mrowietz U, Kragballe K, Reich K *et al.* Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**: 1–10.
31 van Geel MJ, van de Kerkhof PC, Oostveen AM, de Jong EM, Seyger MM. Fumaric acid esters in recalcitrant pediatric psoriasis: a prospective, daily clinical practice case series. *J Dermatolog Treat* 2016; **27**: 214–220.
32 Steinz K, Gerdes S, Domm S, Mrowietz U. Systemic treatment with fumaric acid esters in six paediatric patients with psoriasis in a psoriasis centre. *Dermatology* 2014; **229**: 199–204.
33 Gerdes S, Domm S, Mrowietz U. Long-term treatment with fumaric acid esters in an 11-year-old male child with psoriasis. *Dermatology* 2011; **222**: 198–200.
34 Bronckers I, Seyger MMB, West DP *et al.* Safety of systemic agents for the treatment of pediatric psoriasis. *JAMA Dermatol* 2017; **153**: 1147–1157.
35 Balak DM, Oostveen AM, Bousema MT *et al.* Effectiveness and safety of fumaric acid esters in children with psoriasis: a retrospective analysis of 14 patients from The Netherlands. *Br J Dermatol* 2013; **168**: 1343–1347.
36 Reich K, Hartl C, Gambichler T, Zschocke I. Retrospective data collection of psoriasis treatment with fumaric acid esters in children and adolescents in Germany (KIDS FUTURE study). *J Dtsch Dermatol Ges* 2016; **14**: 50–58.
37 European Medicines Agency. Skilarence, INN-dimethyl fumarate: Summary of Product Characteristics. European Medicines Agency, London, 2017.
38 Thaci D, Weisenseel P, Philipp S *et al.* Efficacy and safety of fumaric acid esters in patients with psoriasis on medication for comorbid conditions—a retrospective evaluation (FACTS). *J Dtsch Dermatol Ges* 2013; **11**: 429–435.
39 Lijnen R, Otters E, Balak D, Thio B. Long-term safety and effectiveness of high-dose dimethylfumarate in the treatment of moderate to severe psoriasis: a prospective single-blinded follow-up study. *J Dermatolog Treat* 2016; **27**: 31–36.
40 Ismail N, Collins P, Rogers S, Kirby B, Lally A. Drug survival of fumaric acid esters for psoriasis: a retrospective study. *Br J Dermatol* 2014; **171**: 397–402.
41 Gollnick H, Altmeyer P, Kaufmann R *et al.* Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. *Dermatology* 2002; **205**: 46–53.
42 Weisenseel P, Reich K, Griemberg W *et al.* Efficacy and safety of fumaric acid esters in combination with phototherapy in patients with moderate-to-severe plaque psoriasis (FAST). *J Dtsch Dermatol Ges* 2017; **15**: 180–186.
43 Tzaneva S, Geroldinger A, Trattner H, Tanew A. Fumaric acid esters in combination with a 6-week course of narrowband ultraviolet B provides an accelerated response compared with fumaric acid esters monotherapy in patients with moderate-to-severe plaque psoriasis: a randomized prospective clinical study. *Br J Dermatol* 2018; **178**: 682–688.
44 Mrowietz U, Szepietowski JC, Loewe R *et al.* Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm(®)- and placebo-controlled trial (BRIDGE). *Br J Dermatol* 2017; **176**: 615–623.

45 Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. *Br J Dermatol* 1998; **138**: 456–460.
46 O'Gorman J, Russell HK, Li J, Phillips G, Kurukulasuriya NC, Viglietta V. Effect of aspirin pretreatment or slow dose titration on flushing and gastrointestinal events in healthy volunteers receiving delayed-release dimethyl fumarate. *Clin Ther* 2015; **37**: 1402–1419.
47 Sheikh SI, Nestorov I, Russell H *et al.* Tolerability and pharmacokinetics of delayed-release dimethyl fumarate administered with and without aspirin in healthy volunteers. *Clin Ther* 2013; **35**: 1582–1594.
48 Balak DM, Fallah Arani S, Hajdarbegovic E *et al.* Efficacy, effectiveness and safety of fumaric acid esters in the treatment of psoriasis: a systematic review of randomized and observational studies. *Br J Dermatol* 2016; **175**: 250–262.
49 Sweetser MT, Dawson KT, Bozic C. Manufacturer's response to case reports of PML. *N Engl J Med* 2013; **368**: 1659–1661.
50 Balak DMW, Hajdarbegovic E, Bramer WM, Neumann HAM, Thio HB. Progressive multifocal leukoencephalopathy associated with fumaric acid esters treatment in psoriasis patients. *J Eur Acad Dermatol Venereol* 2017; **31**: 1475–1482.
51 Rosenkranz T, Novas M, Terborg C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. *N Engl J Med* 2015; **372**: 1476–1478.
52 Ermis U, Weis J, Schulz JB. PML in a patient treated with fumaric acid. *N Engl J Med* 2013; **368**: 1657–1658.
53 van Oosten BW, Killestein J, Barkhof F, Polman CH, Wattjes MP. PML in a patient treated with dimethyl fumarate from a compounding pharmacy. *N Engl J Med* 2013; **368**: 1658–1659.
54 Gieselbach RJ, Muller-Hansma AH, Wijburg MT *et al.* Progressive multifocal leukoencephalopathy in patients treated with fumaric acid esters: a review of 19 cases. *J Neurol* 2017; **264**: 1155–1164.
55 Reich K, Hartung HP, Lebwohl M. More on PML in patients treated with dimethyl fumarate. *N Engl J Med* 2016; **374**: 294–295.
56 Mrowietz U, Reich K. Case reports of PML in patients treated for psoriasis. *N Engl J Med* 2013; **369**: 1080–1082.
57 Saribas AS, Ozdemir A, Lam C, Safak M. JC virus-induced progressive multifocal leukoencephalopathy. *Future Virol* 2010; **5**: 313–323.
58 Ogilvie S, Lewis Jones S, Dawe R, Foerster J. Proteinuria with fumaric acid ester treatment for psoriasis. *Clin Exp Dermatol* 2011; **36**: 632–634.
59 Menzies S, Ismail N, Abdalla A *et al.* Renal dysfunction in patients taking fumaric acid esters – a retrospective cross-sectional study. *J Eur Acad Dermatol Venereol* 2017; **31**: 686–691.
60 Park JI, Baek H, Kim BR, Jung HH. Comparison of urine dipstick and albumin:creatinine ratio for chronic kidney disease screening: a population-based study. *PLoS ONE* 2017; **12**: e0171106.
61 KDIGO 2012. Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; **3**: 1–150.
62 Balak DM. Fumaric acid esters in the management of psoriasis. *Psoriasis (Auckl)* 2015; **5**: 9–23.
63 Hu SC, Lan CE. Psoriasis and cardiovascular comorbidities: focusing on severe vascular events, cardiovascular risk factors and implications for treatment. *Int J Mol Sci* 2017; **18**: 2211.
64 Feldman SR, Goffe B, Rice G *et al.* The challenge of managing psoriasis: unmet medical needs and stakeholder perspectives. *Am Health Drug Benefits* 2016; **9**: 504–513.
65 Mrowietz U, Elder JT, Barker J. The importance of disease associations and concomitant therapy for the long-term management of psoriasis patients. *Arch Dermatol Res* 2006; **298**: 309–319.
66 von Hehn C, Howard J, Liu S *et al.* Immune response to vaccines is maintained in patients treated with dimethyl fumarate. *Neurol Neuroimmunol Neuroinflamm* 2018; **5**: e409.
67 Susitaival P, Winhoven SM, Williams J *et al.* An outbreak of furniture related dermatitis ('sofa dermatitis') in Finland and the UK: history and clinical cases. *J Eur Acad Dermatol Venereol* 2010; **24**: 486–489.
68 Rantanen T. The cause of the Chinese sofa/chair dermatitis epidemic is likely to be contact allergy to dimethylfumarate, a novel potent contact sensitizer. *Br J Dermatol* 2008; **159**: 218–221.
69 Ruggieri S, Tortorella C, Gasperini C. Pharmacology and clinical efficacy of dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis. *Ther Clin Risk Manag* 2014; **10**: 229–239.
70 Atwan A, Ingram JR, Abbott R *et al.* Oral fumaric acid esters for psoriasis: abridged Cochrane systematic review including GRADE assessments. *Br J Dermatol* 2016; **175**: 873–881.
71 Balasubramaniam P, Stevenson O, Berth-Jones J. Fumaric acid esters in severe psoriasis, including experience of use in combination with other systemic modalities. *Br J Dermatol* 2004; **150**: 741–746.
72 Heelan K, Markham T. Fumaric acid esters as a suitable first-line treatment for severe psoriasis: an Irish experience. *Clin Exp Dermatol* 2012; **37**: 793–795.
73 Carboni I, De Felice C, De Simoni I, Soda R, Chimenti S. Fumaric acid esters in the treatment of psoriasis: an Italian experience. *J Dermatolog Treat* 2004; **15**: 23–26.
74 Fallah Arani S, Balak DM, Neumann HA, Kuipers MV, Thio HB. Treatment of psoriasis with non-registered fumaric acid esters in The Netherlands: a nationwide survey among Dutch dermatologists. *J Eur Acad Dermatol Venereol* 2014; **28**: 972–975.
75 Wilsmann-Theis D, Frambach Y, Philipp S *et al.* Systemic antipsoriatic combination therapy with fumaric acid esters for plaque-type psoriasis: report on 17 cases. *Dermatology* 2015; **230**: 119–127.
76 van Bezooijen JS, Balak DM, van Doorn MB *et al.* Combination therapy of etanercept and fumarates versus etanercept monotherapy in psoriasis: a randomized exploratory study. *Dermatology* 2016; **232**: 407–414.
77 Hoefnagel JJ, Thio HB, Willemze R, Bouwes Bavinck JN. Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *Br J Dermatol* 2003; **149**: 363–369.
78 Saurat JH, Guerin A, Yu AP *et al.* High prevalence of potential drug-drug interactions for psoriasis patients prescribed methotrexate or cyclosporine for psoriasis: associated clinical and economic outcomes in real-world practice. *Dermatology* 2010; **220**: 128–137.