Northern Treatment Advisory Group

Dimethyl fumarate for moderate to severe chronic plaque psoriasis

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Summary

- Dimethyl fumarate is an oral fumaric acid ester (FAE) thought to improve psoriasis through immunomodulatory, anti-inflammatory, antioxidant and antiangiogenic effects. A marketing authorisation application is currently under evaluation for treatment of adults with moderate to severe chronic plaque psoriasis requiring systemic therapy.
- An oral compound FAE preparation containing dimethyl fumarate (main active component) and monoethyl fumarate salts (Fumaderm®) is licensed for moderate to severe psoriasis in Germany. Although unlicensed in the UK, Fumaderm® is imported for use by specialist dermatology centres particularly in patients who fail or are intolerant to other non-biological systemic therapy.
- A pivotal phase III RCT compared dimethyl fumarate to placebo and Fumaderm® in 671 adults with moderate to severe plaque psoriasis, aiming to demonstrate superiority of dimethyl fumarate to placebo, and non-inferiority to Fumaderm®. At week 16, dimethyl fumarate was superior to placebo for the co-primary outcomes of Psoriasis Area Severity Index (PASI) 75 (37.5% vs 15.3%) and Physician Global Assessment response of 0 “clear” /1 “almost clear” (33.0% vs 13.0%); and non-inferior to Fumaderm® for PASI 75 (37.5% vs 40.3%, non-inferiority margin ±15%).
- Previous studies on compound FAE therapy also suggest that they are superior to placebo and possibly similar in efficacy to methotrexate but the overall quality of the evidence is low due to limitations such as small patient numbers and use of non-validated outcome measures.
- The rates and types of treatment emergent adverse events (TEAEs) in the pivotal study were similar between the dimethyl fumarate and Fumaderm® groups and consistent with the known safety profile of FAE. TEAEs were mostly considered to be mild but led to discontinuation in nearly a quarter of patients receiving active treatment. The most common adverse effects were GI symptoms (nausea, vomiting, abdominal pain, flatulence, diarrhoea) occurring in about two thirds of patients followed by flushing.
- Reduced leucocyte and lymphocyte counts were also observed. Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients on FAE with severe prolonged lymphopenia. Regular monitoring of full blood count is required during treatment.
- There is lack of data on long-term efficacy and safety of dimethyl fumarate or compound FAE, or on comparison with other systemic treatments. There are currently no data on combining with other systemic treatments.
- If licensed, dimethyl fumarate will provide an additional licensed oral treatment option for psoriasis. The anticipated place in therapy is for patients in whom other systemic therapies (methotrexate, ciclosporin and acitretin) are clinically inappropriate and prior to use of biologics.
- The cost of dimethyl fumarate is not yet available. The manufacturer anticipates it will be a minimum of 10% less expensive than using unlicensed Fumaderm®. Assuming it will be 10% less expensive, this corresponds to an estimated annual maintenance cost of £1,655.64 to £4,966.92 depending on dose.
- As a further oral treatment option, dimethyl fumarate may delay or avoid the need for biologics. Therefore costs could be offset against potential savings realised through reduced use of biologics.

Introduction and background

Psoriasis is a chronic inflammatory skin condition that typically follows a relapsing and remitting course. The most common form, affecting up to 90% of patients is chronic plaque psoriasis characterised by well-demarcated red, scaly plaques varying in extent from a few patches to generalised skin involvement.[1] The impact of psoriasis on appearance and function can significantly affect quality of life.[2]

Psoriasis can be graded as mild, moderate or severe. The most widely used measure of severity is the Psoriasis Area Severity Index (PASI) which takes into account the size of the affected area, redness, thickness and scaling. Others include the percentage of body surface area (BSA) affected and the Physician's Global Assessment (PGA). The Dermatology Life Quality Index (DLQI) is used to assess impact on quality of life (QoL). NICE consider the disease to be severe if PASI and DLQI ≥ 10; European guidelines define moderate to severe disease as PASI or BSA >10 and DLQI >10. These scales are also used to assess treatment efficacy. For instance PASI 75 (≥75 reduction in the PASI score) is generally considered the standard psoriasis efficacy outcome measure in clinical trials.[1-3]

Treatments for psoriasis mainly reduce severity of flare-ups rather than prevent episodes and generally have to be continued long-term.[4] First line treatment options include topical therapies such as corticosteroids, vitamin D and tar preparations. Second line options include phototherapy and non-biological systemic therapy (e.g. ciclosporin, methotrexate and acitretin). Third line options include biological therapies (adalimumab, etanercept, infliximab, secukinumab and ustekinumab).[1, 5] In November 2016, NICE approved the oral phosphodiesterase 4 (PDE4) inhibitor apremilast as an additional treatment option for adults with severe chronic plaque psoriasis under specified conditions.[6]

Dimethyl fumarate is an oral fumaric acid ester (FAE). FAE have been used to treat psoriasis since the 1950s.[7] An oral compound FAE preparation containing dimethyl fumarate (the main active component) and monoethyl fumarate salts marketed as Fumaderm® is licensed for moderate to severe psoriasis in Germany. Although unlicensed in the UK, Fumaderm® is imported for use by specialist dermatology centres across the country particularly in patients who fail or are intolerant to other non-biologic systemic therapy.[3, 8, 9]

Dimethyl fumarate is thought to improve psoriasis through various pathways to elicit immunomodulatory, anti-inflammatory, antioxidant and antiangiogenic effects.[2, 10, 11] Treatment is initiated at a starting dose of 30 mg daily, increased gradually up to a maximum of 720 mg daily in divided doses.[12]

Dimethyl fumarate (Tecfidera®) is licensed in the UK for relapsing remitting multiple sclerosis.[13] It is not currently approved for psoriasis in the UK. A marketing authorisation application is currently under evaluation for treatment of adults with moderate to severe chronic plaque psoriasis in adults requiring systemic therapy.[12, 14] The manufacturer anticipates that it will be used in patients unable to receive other oral systemic therapies (methotrexate, ciclosporin and acitretin) due to lack of efficacy or tolerability, or patient preference, and prior to treatment with biologics. Launch is expected in 2017.[12, 15]

Guidance and related advice

NICE clinical guideline 153 (2012) describes the treatment pathway for psoriasis.[1] Topical therapies including corticosteroids, vitamin D and tar preparations are recommended as first line treatment. Phototherapy may be added if symptoms are not controlled with topical treatments alone. Systemic therapy is recommended when:

- Psoriasis cannot be controlled with topical therapy **and**
- It has a significant impact on physical, psychological or social wellbeing **and**
- One or more of the following apply:
  - psoriasis is extensive (e.g. PASI >10 or BSA >10%) **or**
  - psoriasis is localised and associated with significant functional impairment and/ or high levels of distress **or**
  - phototherapy is ineffective, inappropriate or has failed.

The first choice systemic therapy is methotrexate. Ciclosporin is recommended if rapid or short-term disease control is required or for men and women considering conception. If response to either methotrexate or ciclosporin is inadequate, the other drug may be considered. Acitretin may be considered if both methotrexate and ciclosporin are inappropriate or have failed. Systemic non-biological therapy should be initiated in specialist settings but certain aspects of supervision may be appropriate for shared care.

NICE recently approved an additional non-biological systemic treatment, apremilast as an option for treating severe chronic plaque psoriasis (PASI ≥10 and DLQI >10) in adults whose disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and ultraviolet-A light), or when these treatments are contraindicated or not tolerated under specified conditions.[6]

Biological therapies are recommended as third line options. NICE have published individual Technology Appraisal Guidance recommending the use of adalimumab, etanercept, infliximab, secukinumab and ustekinumab for psoriasis. Most are recommended for severe disease (PASI >10 and DLQI >10) except infliximab which is recommended for very severe disease (PASI >20 and DLQI >18) which has not responded to standard systemic therapies or when these treatments are contraindicated or not tolerated. Biological drugs should be initiated and supervised only by specialists experienced in the diagnosis and treatment of psoriasis.[1, 5]

FAE use is not addressed in the current NICE guidelines. A Technology Appraisal Guidance on dimethyl fumarate for treating moderate to severe plaque psoriasis is expected in November 2017.

The SIGN guideline on diagnosis and management of psoriasis and psoriatic arthritis in adults (2010) recommends that FAE can be considered as an alternative maintenance treatment for patients who have failed or are not suitable for other systemic therapies.[16]

The European S3 guidelines on the systemic treatment of psoriasis vulgaris (2015), recommend FAE as an option among other systemic therapies.[3]

Clinical efficacy

This report considers the evidence for dimethyl fumarate monotherapy for moderate to severe psoriasis, and also briefly considers the available evidence for compound FAE therapy since their main active component is dimethyl fumarate.

Dimethyl fumarate monotherapy

Pivotal study

A pivotal 16 week phase III multicentre, randomised, double-blind study of the efficacy and safety of dimethyl fumarate compared to placebo and Fumaderm® in adults with moderate to severe chronic plaque psoriasis (BRIDGE) has been published.[10]

Patients were aged ≥18 years with a diagnosis of chronic plaque psoriasis for at least 12 months, who had PASI >10, BSA >10% and PGA ≥3. Mean baseline PASI score was about 16 and BSA about 22%. Exclusion criteria mentioned in the publication included previous failure on FAE due to lack of efficacy or tolerability, baseline leucocyte counts < $3x10^9$/L and/or lymphocyte counts < $1x10^9$/L, pregnancy and breastfeeding. However, it was later discovered that there were several other exclusion criteria which were not mentioned or made reference to in the main publication.[17, 18] These included patients with severe renal impairment, abnormal liver enzymes (>2x upper limit of normal), significant gastrointestinal (GI) problems (e.g. ulcers, diarrhoea), active infectious disease, HIV or any other immunosuppressive disease and history of malignancies (except non-melanoma skin cancer).

Previously treated patients went through a washout period (2 weeks for topical treatments, 1 month for conventional systemic drugs and phototherapy, 3 months for biologics). Topical and/or additional systemic treatments were not permitted during the trial.

The study enrolled 839 patients of which 704 were randomised in a 2:2:1 ratio to receive dimethyl fumarate, Fumaderm® or placebo for a 16 week treatment period followed by a 12 month off-treatment follow up period to assess safety, rebound and persistence of effect. Treatment was titrated gradually over 9 weeks with placebo or up to a maximum daily dose of 720 mg dimethyl fumarate in the dimethyl fumarate or Fumaderm® groups in line with routine clinical practice. A reduction to the last tolerated dose was permitted after 4 weeks in case of intolerability.

Co-primary outcomes were PASI 75 response and PGA response of “0” (clear) or “1” (almost clear) at week 16. The study aimed to demonstrate superiority of dimethyl fumarate to placebo with respect to PASI 75 and PGA 0/1 response, and non-inferiority to Fumaderm® based on PASI 75 response alone. The non-inferiority margin was set at ±15%. Secondary endpoints included amongst others PASI 50 and PASI 90 at week 16 and DLQI at week 16 and at 2 months follow up.

Efficacy results were reported based on the Full Analysis Set (FAS) which consisted of all randomised patients who received at least one dose of trial medicine with at least one measurement of PASI and PGA score after Week 0. A total of 450 patients completed the treatment phase and 671 patients (95.4%) were included in the FAS. The per protocol set (PPS) analysis was not reported but was said to be consistent.

At week 16, significantly more patients on dimethyl fumarate achieved PASI 75 compared to placebo (see table 1). The difference in PASI 75 response rates between dimethyl fumarate and Fumaderm® was 2.8% (99.24% CI -14.0% to +8.4%, p <0.001) demonstrating non-inferiority. More patients on dimethyl fumarate achieved clear or almost clear PGA scores

compared to placebo. Dimethyl fumarate was similarly superior to placebo with respect to the secondary outcomes PASI 50 and PASI 90.

Table 1. Primary and secondary outcomes at week 16 in BRIDGE study (FAS)

Outcomes	Dimethyl fumarate (DMF) N = 267	Fumaderm® N = 273	Placebo N = 131	Difference (Confidence Interval) DMF vs placebo	Difference (Confidence Interval) DMF vs Fumaderm® (non-inferiority)	*p* value
PASI 75	37.5%	40.3%	15.3%	22.2% (99.24% CI 10.7% - 22.7%)	2.8% (99.24% CI -14.0% to 8.4%)	<0.001 (for both)
PGA 0/1	33.0%	37.4%	13.0%	20.0% (99.24% CI 9.0% - 31.0%)		<0.001
PASI 50	53.6%	61.9%	29.0%	24.6% (95% CI 14.7% - 34.4%)		<0.001
PASI 90	18.4%	22.3%	4.6%	13.8% (95% CI 7.9% - 19.6%)		<0.001

Statistical comparison between dimethyl fumarate and Fumaderm® was only conducted for PASI 75 response. For most other outcomes, response rates were similar between dimethyl fumarate and Fumaderm® although slightly numerically lower with dimethyl fumarate by about 3-4%. Results for the DLQI were published separately as a conference abstract. Mean baseline DLQI score was 11.5. At week 16, patients on dimethyl fumarate had better DLQI scores compared to placebo (5.4 vs 8.5, p<0.0001) and similar scores to those on Fumaderm® (6.0).[19] The only data reported with regards to the off-treatment phase was that the rate of rebound (defined as PASI≥125%) at 2 months after treatment (secondary outcome) was low with dimethyl fumarate and Fumaderm® compared with placebo (1.1%, 2.2% and 9.3% respectively). It is not clear how many patients completed this follow-up phase.

Limitations of BRIDGE study

No justification was provided for the non-inferiority margin of ±15%. The study population was predominantly white (almost 100%), with a mean age of about 45 years; it is not clear what proportion of patients were elderly. Due to the short duration of 16 weeks for the treatment phase of which the first 9 weeks was the titration period, the study may not have allowed sufficient time to demonstrate the maximum effect of treatment. Moreover, long-term efficacy could not be established which is important since psoriasis treatment is usually given long-term in routine clinical practice. The trial excluded patients who had previously failed to respond to FAE. This introduces selection bias, since selected patients may have been more likely to respond to treatment with either dimethyl fumarate or Fumaderm®. The trial also excluded patients with severe renal impairment, liver impairment and immunosuppressive disease. The study was sponsored by the manufacturer Almirall S.A. and two of the authors were Almirall employees at the time of publication.

Other studies

A phase III double-blind RCT comparing a novel formulation of dimethyl fumarate (BG-12) to placebo for moderate to severe plaque psoriasis (n=175) found that after 16 weeks, the median PASI score (primary outcome) was significantly lower with dimethyl fumarate 720

mg/day compared to placebo (5.8 vs 14.2, P < 0.001). PASI 75 was attained by 39% of patients in the dimethyl fumarate group compared to 1% in the placebo group. QoL measured with Skindex-29 (range 0 to 100; higher scores indicate lower QoL) reduced from 54.7 at baseline to 27 at week 16 in the dimethyl fumarate group and from 54.0 to 51.1 in the placebo group (p < 0.001), representing a 47% improvement. No safety results were reported. This study has only been published as an abstract.[20]

Two earlier small studies from the 1990s that compared dimethyl fumarate monotherapy with compound FAE therapy found no statistically significant differences between the two. However, the studies used different dose schedules which differed somewhat from current clinical practice, and did not use validated outcome measures. Consequently, no clear conclusions could be drawn from them.[21, 22]

Compound FAE therapy

Despite the long history of use of FAE for psoriasis, their development was not based on high quality data.[11] Studies evaluating their use have not always used recommended outcome measures, generally involve small patient numbers, and reporting of methodology and results is poor in many.

A recent Cochrane review evaluated the efficacy and safety of oral FAE for psoriasis.[2] Six RCTs with a total of 544 participants were included. Three studies compared compound FAE therapy to placebo, two compared dimethyl fumarate monotherapy to placebo (one of which is described above[20] and another phase II dose finding study), and one compared compound FAE therapy with methotrexate. Only two of these studies were published in full reports; two were published as abstracts, one in a brief communication, and one in a letter. The incompletely reported studies were included because of the overall lack of eligible RCTs.

The review concluded that there was low quality evidence indicating superiority of FAE over placebo after 12 to 16 weeks of treatment and very low quality evidence suggesting possible similarity in efficacy to methotrexate after 12 weeks. The authors advise caution when interpreting the results due to the several limitations of included studies such as insufficient reporting, unclear risk of bias, relatively small patient numbers, and lack of opportunity for meta-analyses due to significant outcome measure heterogeneity. Meta-analysis was possible for PASI 50 from two studies (n=247) and showed superiority of FAE over placebo (risk ratio (RR) 4.55, 95% CI 2.80-7.40; low-quality evidence). However, PASI 75 has superseded PASI 50 as the standard psoriasis outcome measure. In the same two studies, more participants attained PASI 75 than placebo (39%-42% vs 1-11%) but the data were not pooled due to heterogeneity. QoL was reported in just one study – described above.[20] It couldn't be established from the available data whether dimethyl fumarate monotherapy was similar in efficacy and safety as compound FAE therapy.

Another recent systematic review found from 7 RCTs (n=449) that overall, FAE led to a reduction in mean PASI of 42–65% after 12–16 weeks of treatment. Where reported, PASI 75 response was about 20%. The review also included 37 observational studies (n=3457) reporting a wide range in efficacy outcomes; mean reductions in PASI ranged from 13-86% and PASI 75 responses ranged from 8-33% after 12 to 16 weeks of treatment. The reviewers reached a similar conclusion to the Cochrane review and cited similar limitations in the available data including the fact that meta-analysis was not possible owing to considerable heterogeneity.[11]

Summary of clinical efficacy

Dimethyl fumarate was superior to placebo and non-inferior to Fumaderm® for PASI 75 response in the pivotal BRIDGE trial. Available data on compound FAE therapy suggests that they are superior to placebo and possibly similar to methotrexate, but the overall quality of the available evidence is low. There is lack of data on long-term use and comparison with other systemic treatments for psoriasis. Also, there are currently no data on combining with other systemic treatments.

Safety

In the BRIDGE study, the rates and types of adverse events were similar between the dimethyl fumarate and Fumaderm® groups and were consistent with the known side effect profile of FAE; no unexpected safety issues were detected.[3, 10] Table 2 summarises the treatment emergent adverse events (TEAEs) at week 16 in the safety analysis set (all patients receiving at least one dose of trial medication, n=699).

Table 2. Summary of TEAEs at week 16 (safety analysis set)

AE category	Dimethyl fumarate (n=279)	Fumaderm® (n=283)	Placebo (n=137)
Any TEAE, n (%)	234 (83.9)	238 (84.1)	82 (59.9)
Any serious TEAE, %	3.2	2.8	3.6
Discontinuation due to TEAE, n (%)	64 (23)	70 (24)	6 (4)
AEs reported by ≥ 5% of patients in any group, n (%)			
Diarrhoea	108 (38.7)	113 (39.9)	23 (16.8)
Upper abdominal pain	56 (20.1)	64 (22.6)	11 (8.0)
Abdominal pain	55 (19.7)	45 (15.9)	7 (5.1)
Nausea	30 (10.8)	24 (8.5)	5 (3.6)
Flatulence	15 (5.4)	16 (5.7)	7 (5.1)
Vomiting	13 (4.7)	19 (6.7)	2 (1.5)
Pruritus	24 (8.6)	28 (9.9)	15 (10.9)
Erythema	27 (9.7)	23 (8.1)	3 (2.2)
Skin burning sensation	22 (7.9)	20 (7.1)	3 (2.2)
Nasopharyngitis	18 (6.5)	23 (8.1)	13 (9.5)
Flushing	51 (18.3)	46 (15.3)	2 (1.5)
Lymphopenia	28 (10.0)	30 (10.6)	0
Eosinophilia	25 (9.0)	17 (6.0)	0
Headache	23 (8.2)	23 (8.1)	14 (10.2)

The majority of TEAEs were considered to be mild in intensity but there was a high rate of discontinuation due to adverse effects.

The most frequently reported TEAEs in both dimethyl fumarate and Fumaderm® groups were GI disorders (62.7% and 63.3% respectively) followed by flushing. Administration with food has been suggested to help improve GI tolerance.[3, 10] Severe GI disease is considered an absolute contraindication to FAE by the European S3 guidelines.

Only 4 of the 23 serious TEAEs, occurring in three patients randomized to Fumaderm® were considered related to treatment (erosive gastritis, gastritis, gastric ulcer and gastroduodenitis). One death was reported in a patient receiving Fumaderm® but was not considered to be treatment-related.

Haematological adverse events

Leucopenia, lymphopenia and transient eosinophilia are recognised adverse effects of FAE.[3]

The mean leucocyte count decreased from baseline by $0.73x10^9$/L, $0.69x10^9$/L and $0.04x10^9$/L in the dimethyl fumarate, Fumaderm® and placebo groups respectively.

The mean lymphocyte count decreased by $0.52x10^9$/L in both dimethyl fumarate and Fumaderm® groups compared to $0.08x10^9$/L in the placebo group. Severe lymphopenia (lymphocyte count < $0.5x10^9$/L) was observed in 1.1% of patients in the dimethyl fumarate group and 0.07% of patients in the Fumaderm® group.

Most cases of lymphopenia occurring with FAE are mild.[11] Patients who develop chronic severe lymphopenia are at increased the risk of opportunistic infections.[3] Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients treated with the licensed dimethyl fumarate preparation for multiple sclerosis (Tecfidera®) and compound FAE therapy including Fumaderm®. PML is a rare, potentially fatal, progressive and demyelinating disease of the central nervous system caused by an opportunistic infection with the John Cunningham (JC) virus. The PML cases usually occurred in patients with prolonged (> 6 months) severe lymphopenia. Both the Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Association (EMA) have issued warnings and recommendations regarding the risks of PML with dimethyl fumarate and other FAE treatments. They advise that patients and carers should be appropriately counselled on the risk of PML and symptoms to watch out for (signs and symptoms of neurological dysfunction e.g. motor, cognitive, or psychiatric symptoms).[3, 10, 23, 24]

Renal and hepatic effects

FAE have been associated with proteinuria and increased serum creatinine levels; cases of acute renal failure and Fanconi syndrome (proximal renal tubular dysfunction) have been reported.[3, 11, 25] Proteinuria was reported in 1.4% of patients in the dimethyl fumarate group and 2.1% in the Fumaderm® group in BRIDGE. Proteinuria is usually transient and/or reversible upon treatment cessation.[3, 11] Mean serum creatinine levels decreased slightly in all treatment groups by 1.11 to 5.18 µmol/L.

Increased hepatic enzymes have also been reported with FAE[3, 11] though the BRIDGE study did not report any measurements of hepatic enzymes.

The European S3 guidelines contraindicate FAE in severe renal or hepatic disease.

Monitoring

Monitoring of full blood count (FBC), renal and hepatic function is recommended at baseline and during FAE treatment.[3, 25] The manufacturer is currently in discussion with regulatory authorities regarding monitoring requirements.[12]

It is recommended that FAE treatment is discontinued immediately if leucocytes fall below $3x10^9$/L. If lymphocytes fall below $0.7x10^9$/L, the dose of FAE should be halved; if the lymphocyte count remains below this value after 2 to 4 weeks, or if lymphocyte count ever drops below $0.5x10^9$/L, treatment must be discontinued.[3, 25] The available follow-up data from BRIDGE showed that white blood cell counts progressively recovered after treatment with either dimethyl fumarate or Fumaderm® was stopped.

The Fumaderm® SPC recommends discontinuing treatment if serum creatinine increases above the normal range.[25]

Limitations to safety data

There were some limitations to the BRIDGE trial safety data. There was a high rate of discontinuation due to adverse effects but no details were provided on the adverse effects that led to discontinuation in different treatment groups. Previous studies have reported discontinuation of FAE mostly due to GI and flushing symptoms.[7, 11] The high rate of adverse events particularly of flushing and GI symptoms in the dimethyl fumarate and Fumaderm® groups may have caused a degree of un-blinding. Finally, due to the short duration of the treatment period, long-term safety could not be established. Safety data for the 52 week off-treatment period are yet to be reported. Few observational studies have specifically evaluated the long-term safety of FAE including a small (n=66) Dutch retrospective study in patients treated with FAE continuously for up to 14 years,[26] and a large (n=984) German study in patients treated for an average of 3.5 years.[27] Overall, the available long-term data do not indicate increased risk for infections (except for patients with drug-induced lymphopenia), malignancies or other serious adverse events with long-term FAE treatment.[3,11] Whilst this is reassuring, there is a need for more robust data.

Specialist opinion

Specialists with experience in using FAE based at The Newcastle upon Tyne Hospitals NHS Foundation Trust have said that the reports of PML in patients on FAE with lymphopenia combined with the availability of better drugs in their experience have led to a reduction in their prescribing of FAE. They still use FAE in patients who have failed standard treatment but who do not qualify for biologics due to a PASI or DLQI score <10. They anticipate that due to cost, dimethyl fumarate will likely be approved only for patients with PASI and DLQI >10 which will limit their use. If priced similar to ciclosporin, they might consider it for patients with PASI 5-10 for use prior to biologics but they would be very strict about monitoring lymphocyte counts which is expected to limit prescribing.[28]

Dosage and administration

Similar to Fumaderm®, dimethyl fumarate tablets will be available in two different strengths of 30 mg and 120 mg. The usual dose regime is to start with 30 mg dimethyl fumarate once daily increased by one tablet weekly. At the fourth week, the 30 mg tablets are discontinued and the patient continues with the 120 mg tablets starting with 120 mg once daily increased by one tablet weekly up to a maximum of 720 mg daily in 3 divided doses. Following clinical improvement, the dose is then reduced gradually to an individualised maintenance dose.[10, 12]

Cost analysis

The cost of dimethyl fumarate treatment for psoriasis is yet to be finalised. The manufacturer is currently conducting an economic analysis to determine the cost-effective price in the UK.[12]

The manufacturer anticipates that dimethyl fumarate will be a minimum of 10% less expensive than unlicensed use of FAE. The list price for Fumaderm® in Germany is €2.43 per 120 mg tablet which is equivalent to £2.07 assuming an exchange rate of €1 = £0.85 (15th February 2017). Taking into account import charges, the estimated overall cost is about £2.52 per 120 mg tablet.[12] Table 3 shows the estimated annual treatment cost per patient of varying maintenance doses of Fumaderm® and the corresponding estimated cost of dimethyl fumarate assuming it will cost 10% less than imported Fumaderm®.

Table 3. Estimated annual cost per patient

Number of 120 mg tablets per day	Estimated annual cost of Fumaderm® (acquisition + import charges)	Estimated annual cost of dimethyl fumarate (assuming 10% less expensive than imported Fumaderm®
2	£1,839.60	£1,655.64
3	£2,759.40	£2,483.46
4	£3,679.20	£3,311.28
5	£4,599.00	£4,139.10
6	£5,518.80	£4,966.92

At week 16 in the BRIDGE trial, most patients were taking between 5 to 6 tablets of 120 mg dimethyl fumarate daily.

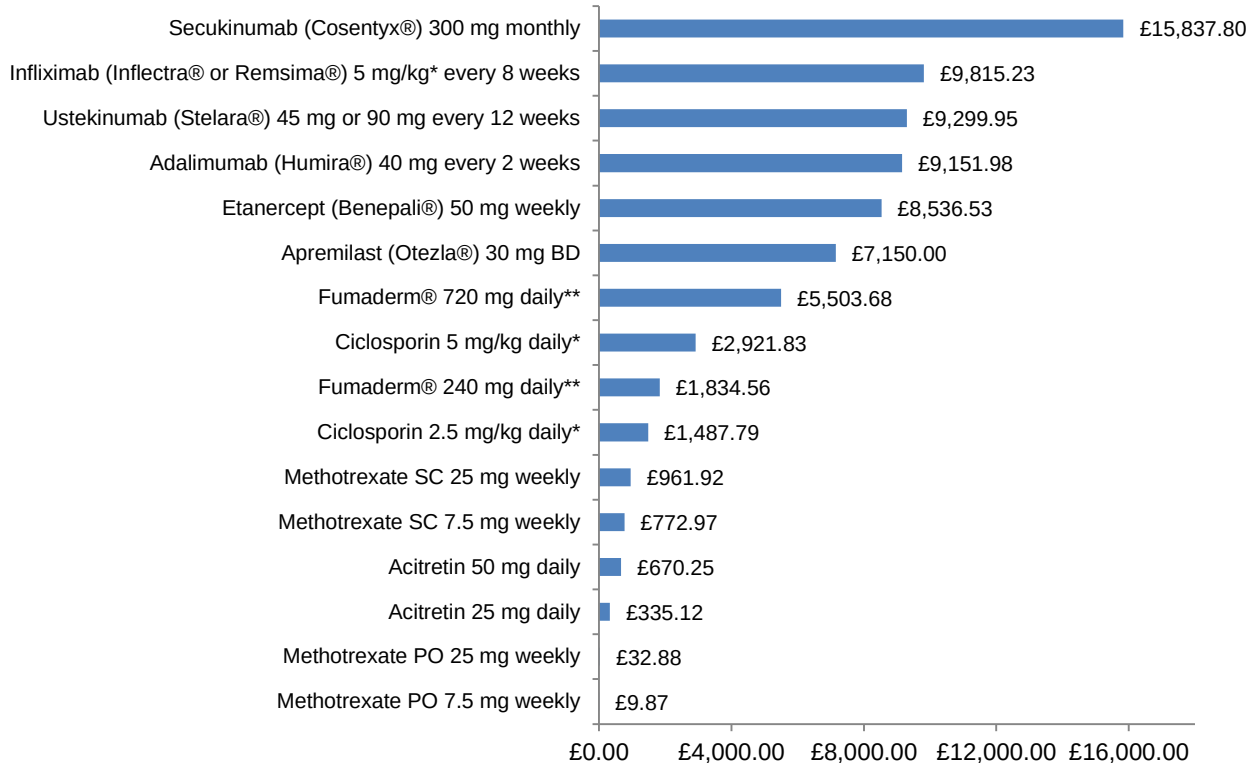
NICE estimates that the prevalence of psoriasis in England is 1.75%. About 20% have moderate to severe disease (15% moderate, 5% severe) which equates to about 350 per 100,000 population. Based on an adult (≥18 years) population of around 2.51 million, this equates to approximately 8,785 adults who could be eligible for dimethyl fumarate across the NTAG area.

As an additional licensed oral treatment option, dimethyl fumarate may delay or avoid the need for biologics. Therefore costs could be offset against potential savings realised through reduced use of biologics.

For information only, the licensed dimethyl fumarate product for multiple sclerosis Tecfidera® is available as 120 mg tablets (used for a 7 day titration period) and 240 mg tablets (for maintenance). The 120 mg tablets cost £343.00 per pack of 14.[29] Tecfidera® is manufactured by a different company to Almirall.

The chart below compares annual maintenance cost of psoriasis treatments.

Fig 1. Annual maintenance cost per patient of psoriasis drugs (Drug Tariff /dm+d, February 2017)



Prices are for comparison only and do not imply therapeutic equivalence. Prices do not include any local discounts or costs associated with administration.

* Based on a 70 kg adult

** Includes acquisition cost and import charges

Points to consider

- The pivotal BRIGDE trial demonstrated the superiority of dimethyl fumarate to placebo with respect to PASI 75 and PGA 0/1, and non-inferiority of dimethyl fumarate to Fumaderm® with respect to PASI 75.
- Previous studies on compound FAE treatment also suggest that they are superior to placebo and possibly similar in efficacy to methotrexate but the quality of evidence is low.
- Rates and types of adverse effects were similar with dimethyl fumarate and Fumaderm® groups and consistent with the known safety profile of FAE. Although most side effects are considered mild, they can lead to high rates of treatment discontinuation.
- Lymphopenia occurred in about 10% of patients receiving active treatment. The MHRA and EMA have issued warnings regarding cases of PML reported in patients on FAE with severe prolonged lymphopenia. Regular monitoring of full blood count is required during treatment.
- The study population in the BRIDGE study was predominantly white (almost 100%) with a mean age of about 45 years; the proportion of elderly patients was not clear. Patients with immunosuppressive disease and with severe renal and hepatic disease were excluded.
- The study duration was too short to establish long-term efficacy or safety. Few observational studies have specifically evaluated long-term use. While the available

data is assuring, more data from larger, well conducted studies of sufficient duration are required to fully establish long-term efficacy and safety.

- Studies comparing FAE with other systemic treatments are lacking. Only one such RCT was identified which suggested that FAE are potentially similar in efficacy to methotrexate. Also, there are currently no data on combining with other systemic treatments.
- If licensed, dimethyl fumarate will provide an additional oral treatment option which patients may find more acceptable than other treatments given by injection.
- The anticipated place in therapy is for patients in whom other systemic therapies are clinically inappropriate (methotrexate, ciclosporin and acitretin) and prior to use of biologics.
- Specialists at Newcastle University Teaching Hospitals indicate that due to reports of PML and availability of better drugs in their experience, their prescribing of FAE has reduced. They are still used for patients who have failed standard treatment but who do not qualify for biologics due to a PASI or DLQI score <10.
- The cost of dimethyl fumarate is not yet available. The manufacturer is currently conducting an economic analysis to determine the cost-effective price in the UK. They anticipate that dimethyl fumarate will be at least 10% cheaper than unlicensed FAE use. Assuming it will be 10% less expensive, this corresponds to an estimated annual maintenance cost of £1,655.64 to £4,966.92 depending on dose.
- Costs may be offset by potential savings realised through reduced use of biological therapies.
- A NICE Technology Appraisal Guidance on dimethyl fumarate for treating moderate to severe plaque psoriasis is expected in November 2017.

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