Fumaderm®: what is the evidence for its efficacy and safety in treating psoriasis?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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Date prepared: October 2015

Summary

- Fumaderm® (fumaric acid esters) tablets are licensed in Germany for treating adults with moderate to severe plaque psoriasis for whom topical therapy is ineffective. Although unlicensed in the UK, Fumaderm® is used by specialist dermatology centres.
- Limited evidence, including only two randomised controlled trials, indicates that Fumaderm® is beneficial in patients with moderate to severe chronic plaque psoriasis; at least 50% of patients treated with Fumaderm® have a reduction of about 70% or more in Psoriasis Area and Severity Index (PASI) score after 16 weeks of treatment. Patients with recalcitrant disease are less likely to achieve significant improvement, but many can stop, or reduce the dose of, concomitant systemic anti-psoriasis agents. There is insufficient data to recommend Fumaderm® for mild psoriasis.
- Data from controlled and observational studies show Fumaderm® is effective as a first-line systemic agent in patients not responding to topical therapy, as an alternative to other systemic agents that are ineffective or not tolerated, and in combination with oral drugs in patients with recalcitrant disease.
- Adverse effects, including diarrhoea, abdominal pain and facial flushing, are common at the start of treatment with Fumaderm® and lead to discontinuation and/or non-compliance in 30 to 40% of patients. Reversible leucopenia, lymphopenia and transient eosinophilia are frequently observed; long-lasting lymphopenia increases risk of opportunistic infections including progressive multi-focal leukoencephalopathy. Lymphocyte and leucocyte counts must be regularly monitored.
- Proteinuria, and increases in serum creatinine and liver enzymes occur rarely and usually resolve with continued treatment or on dose reduction.

Background

Fumaric acid esters (FAE) have been used to treat psoriasis since 1959 [1]. An oral preparation containing dimethyl fumarate and monoethyl fumarate salts, Fumaderm®, is licensed in Germany for treating adults with moderate to severe plaque psoriasis in whom topical therapy is not effective [2,3]. It is available in two strengths, Fumaderm® initial 105mg tablets (containing 30mg dimethyl fumarate) and Fumaderm® 215mg tablets (containing 120mg dimethyl fumarate). Patients start on 105mg once daily and the dose is increased weekly by one tablet to a maximum of 1,290mg daily (six tablets) in three divided doses (equivalent to 720mg dimethyl fumarate) [3]. Although unlicensed, Fumaderm® is used in the UK by specialist dermatology centres to treat psoriasis [4-5]. Despite rare reports of renal toxicity [6-8], Fumaderm® is considered safer than other commonly used systemic agents [1,2,8-9]. European guidelines recommend FAE as one of a number of systemic treatments for psoriasis in adults [10]; however in the UK it is suggested they should be restricted to patients who find other systemic treatments unsuitable or ineffective [11]. As an unlicensed drug, FAE have not been included in guidelines produced by the National Institute for Health and Care Excellence [12].

This Medicines Q&A reviews evidence for efficacy and safety of Fumaderm® in treating psoriasis.

Answer

Efficacy data

Randomised trials

Two small double-blind randomised placebo-controlled trials showed Fumaderm® to be effective in treating patients with moderate to severe psoriasis over 16 weeks [13,14]. In the first study involving 27 men and 12 women with psoriasis (type not specified; age 20 to 73 years) Fumaderm® reduced mean percentage body surface area (BSA) affected from 21% at baseline to 6.7%, which was significant compared to

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placebo and monoethylfumarates (no data for comparators; p<0.01) [13]. Six (50%) of 12 patients on Fumaderm® achieved complete clearance and three showed improvement; only one of 12 patients in the placebo group showed improvement. Mean scores for infiltration and scaling were also significantly lower in patients on Fumaderm® compared with those on placebo and monoethylfumarates (no data reported; p<0.01). All patients additionally received topical salicylic acid 5% in white soft paraffin and were asked to follow a strict diet, avoiding nuts, spices, wines and distilled wine products. Fumaderm® was started at a dose of 215mg daily and gradually increased to 1,290mg. No information was provided on previous psoriasis treatments.

The second study recruited 100 patients (aged 19 to 69 years) with moderate to severe chronic plaque, guttate, pustular or erythrodermic psoriasis who were insufficiently or no longer responsive to topical therapies [14]. Compared with placebo, Fumaderm®, increased in weekly increments from a daily dose of 105mg to 1,290mg, reduced mean Psoriasis Area and Severity Index (PASI) score from a baseline of 21.57 to 10.77 after 16 weeks (p<0.0001), whereas mean PASI score in the placebo group was unchanged (placebo data shown only in a graph). Fumaderm® was reported to significantly alleviate arthralgia (p<0.002 vs. placebo), but not nail changes, however no data were presented. Patients were allowed to use emollients but other topical anti-psoriasis preparations were withdrawn two weeks before the study began. Using graphical data from this study, a systematic review of treatments for severe psoriasis calculated that 28 (57%) of 49 patients in the Fumaderm® group achieved at least a 70% reduction in PASI score (PASI-70) compared with only five (10%) of 50 patients in the placebo group (response rate difference 0.47 [95% confidence interval (CI) 0.31 to 0.63]) [15]. A meta-analysis also used data from this study to indirectly compare efficacy of Fumaderm® with other systemic therapies [16]. The authors concluded that Fumaderm® was as effective as etanercept 50mg twice weekly in achieving at least a PASI-75 response (risk difference vs. placebo, 0.48 [0.32 to 0.64] and 0.44 [0.40 to 0.48], respectively). However wide confidence intervals for the Fumaderm® data, reflecting small patient numbers, reduce reliability of these findings. Fumaderm® also had the highest mean monthly rate of withdrawal than any other therapy (10.2% vs. etanercept 0.6% and methotrexate 7.3%).

One open-label active comparator study showed short-term therapy with FAE is as effective as methotrexate in patients with moderate to severe chronic plaque psoriasis [17]. This study used a Dutch preparation (Magistrale Bereider Oud-Beijerland), similar to Fumaderm®. Intention-to-treat analysis of data from 51 adults who stopped all prior topical therapies (except emollients) and systemic anti-psoriasis agents, showed mean PASI decreased from 18.1 to 10.5 after 12 weeks in those randomised to FAE and from 14.5 to 6.7 in those receiving methotrexate 15mg once weekly (baseline-adjusted absolute difference 1.4 [-2.0 to 4.7]; p=0.417). PASI-75 response was achieved by five (19%) patients on FAE and by six (24%) on methotrexate; 11 (42%) and 15 (60%), respectively, had a 50% or greater decrease in PASI. After 12 weeks, the dose of methotrexate was tapered, and at 16 weeks, both FAE and methotrexate were stopped. Follow-up analysis at 20 weeks showed no patients in the FAE group had a worsening of their psoriasis and seven (39%) and 13 (72%) achieved a PASI-75 and PASI-50 response, respectively; in the methotrexate group, three patients had a worsening in PASI score, and six (32%) and ten (53%) achieved a PASI-75 and PASI-50 response, respectively. Five patients in the FAE group and three patients in the methotrexate group withdrew because of adverse events.

A Cochrane review of oral FAE for psoriasis concluded that limited evidence suggests FAE are superior to placebo and possibly have similar efficacy to methotrexate [18]. The review included data for 544 patients from six studies — the three randomised trials described above [13,14,17] plus a placebo-controlled study in patients with psoriatic arthritis (and also psoriasis) and two studies comparing a different FAE preparation (dimethyl fumarate alone) with placebo. Meta-analysis of PASI score data was not possible for FAE compared with placebo because of differences in how this outcome was reported. Numbers of patients on FAE and methotrexate who achieved PASI-50, PASI-75 and PASI-90 responses were similar, as were dropout rates due to adverse effects. Another systematic review (updating the meta-analysis described above [16]) that includes two of the above studies [14,17] came to the same conclusions as Cochrane [19].
Observational studies
A number of open-label observational studies involving patients aged between 14 and 105 years have been published [20-36]. Two case series and three case reports involving a total of 23 children aged between six and 17 years have also been published [37-40] (see Appendix One). These papers provide data on long-term efficacy of FAE, use in children, and use in combination with topical and other systemic agents (concomitant use with other systemic anti-psoriasis agents is not recommended by the manufacturer [3]) and phototherapy. Like the trials above, many do not provide sufficient detail of baseline disease. However, several used a recommended combination of outcome measures, e.g. PASI score and Physician’s Global Assessment (PGA) of improvement (see European Medicines Agency [EMA] guidance [41]), and some studies measured impact on quality of life using a validated scale.

Summary of efficacy evidence
The evidence, although limited, indicates that Fumaderm® will provide benefit to patients with moderate to severe chronic plaque psoriasis; at least 50% of patients treated with Fumaderm® will have a reduction of about 70% or more in PASI score after 16 weeks of treatment [13,14,42]. The benefits of treatment appear to be sustained over many months to years [5,6,9,25-32]. Patients with recalcitrant disease are less likely to achieve significant improvement in their psoriasis, but many can stop, or reduce the dose of, concomitant systemic anti-psoriasis agents [33-35]. Fumaderm® is effective as a first-line systemic agent in patients with moderate or severe psoriasis not responding to topical therapy, as an alternative to other systemic agents that are ineffective or not tolerated, and in combination with oral drugs in patients with recalcitrant disease. Five studies included patients with mild psoriasis (n=55) but data are insufficient to recommend Fumaderm® for mild disease [26,27,28,31,32]. All controlled trials excluded patients with gastrointestinal and cardiovascular disease, and those with impaired liver or renal function or who were pregnant; four observational studies reported outcomes in some of these patient groups [23,26,31,32].

Safety data
Adverse effects are common when starting Fumaderm® and lead to discontinuation and/or non-compliance in 30 to 40% of patients [2]. Two thirds of patients experience gastrointestinal symptoms of diarrhoea, abdominal pain and flatulence and one third report facial flushing lasting minutes to hours, sometimes associated with headache [2,15]. These adverse effect rates occur despite initial use of low doses and gradual dose increases as recommended by the manufacturer [3]. Dose reduction may alleviate symptoms but Fumaderm® should be stopped if no improvement is seen [2]. Aspirin can help decrease flush symptoms [10]. Fumaderm® can be stopped abruptly as relapse or rebound phenomena do not occur [42].

Reversible leucopenia, lymphopenia and transient eosinophilia are also frequently observed [2]. Leucopenia occurs in a quarter of patients [43]. A mild reduction in lymphocyte count occurs in around 50% of patients [3] and can exceed 50% from baseline in about 10% of patients [15]. It has been reported that patients with lymphopenia are significantly more likely to show improvement in psoriasis than those whose lymphocyte count stays within the normal range [5,21,35]. Eosinophilia occurring between the fourth and tenth week of treatment [42], in up to a third of patients, generally lasts for one to two months and resolves without intervention [5,6,9,13,17,20,21,35,43]. The clinical significance of these changes is not known [35,43]. However, long-lasting lymphopenia increases the risk for opportunistic infections [10]. Several cases of progressive multi-focal leukoencephalopathy (PML) have been reported in patients taking FAE [44-47]; severe prolonged lymphopenia is a risk factor for PML [48,49] and was present in all but one case [47]. Fumaderm® must be stopped immediately if lymphocytes fall below 0.5x10^9/L (500/microL) or leucocytes fall below 3.0x10^9/L (3,000/microL) [3]. If lymphocytes fall below 0.7x10^9/L (700/microL), the dose must be halved; if lymphocyte count remains below 0.7x10^9/L (700/microL) after two to four weeks, treatment must be stopped [3]. In some cases of PML, treatment with FAE had not been stopped when lymphocytes fell below 0.5x10^9/L (500/microL) [44-46]. It has been suggested that cell counts of specific lymphocyte subsets should be assessed as these can fall even if total lymphocyte count exceeds 0.5x10^9/L (500/microL) [50]. There has also been a case of generalised varicella zoster infection that developed two months after treatment with FAE was started for psoriasis; the patient did not have lymphopenia [51].

There have been rare case reports of patients developing acute renal failure or proteinuria when given Fumaderm® [1,2,8,15]. Some studies report raised serum creatinine and/or the presence of urinary protein in up to 30% of patients: in the majority of patients the changes were transient and needed no intervention [6,13,17,26,29,34,38,43]. A case of de Toni-Fanconi syndrome that completely resolved four weeks after FAE were stopped has also been reported [52]. Transient and/or reversible increases in liver enzymes

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and hypercholesterolaemia have also been reported [2,5,6,9,13,17,35,43]. It is recommended that kidney and liver function should be monitored regularly during treatment [3]. If creatinine levels increase above the normal range, Fumaderm® must be stopped [3]. Drugs known to have a harmful effect on kidneys should not be taken with Fumaderm® [3], because FAE may impair renal function [10]. Fumaderm® is not reported to interact with any other drugs [10].

**Limitations**

Evidence for efficacy and safety of Fumaderm® is limited by lack of controlled trial data, especially investigating long-term use or comparison with other systemic therapies. Studies have not used recommended combinations of outcome measures for psoriasis therapies, generally involve small numbers of patients and many poorly document their methods and findings. Patients with serious comorbidity have been excluded from all controlled studies to date. Fumaderm® is not licensed in Germany for use in children, and paediatric data are lacking.

**References**


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33. Wain EM, Ronda L, Barker JNW and Smith CH. Prospective, open, nonrandomized study investigating efficacy and safety of fumaric acid esters in a cohort of patients with severe, recalcitrant, chronic plaque psoriasis. Br J Dermatol 2004; 151 (Suppl. 68): 6 [abstract only].

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Date of check
October 2015

Search strategy (conducted on 7th September 2015)

- Embase ([exp PSORIASIS/] and [exp FUMARIC ACID/ or FUMARIC ACID DERIVATIVE/ or exp DIMETHYLFUMARATE/]); limit human.
- Medline ([exp PSORIASIS/] and [exp FUMARATES/]); limit human.
- Cochrane Library, Issue 9, September 2015 (free text advanced search all text [fuma* and psoriasis]).
- In-house database/ resources.
- NICE Evidence Search Health and Social Care via www.evidence.nhs.uk (free text [psoriasis]).
- British Association of Dermatologists www.bad.org.uk
- Psoriasis Association www.psoriasis-association.org.uk
- DermNet NZ: the dermatological resource www.dermnetnz.org
- National Institute for Health and Care Excellence www.nice.org.uk
- European Medicines Agency www.ema.europa.eu
- Dr John Kellett, Consultant Dermatologist and Dr Walter Bottomley, Consultant Dermatologist, Blackpool, Fylde and Wyre Hospitals NHS Foundation Trust. (Contacted in 2009)
## Appendix One. Observational data on Fumaderm® in psoriasis.

<table>
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<tr>
<th>Study (ref and type)</th>
<th>Patient details</th>
<th>Treatment duration</th>
<th>Study findings</th>
<th>Comments</th>
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<tr>
<td><strong>Short-term studies &lt; six months (total n=537)</strong></td>
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<td></td>
<td>Mean PASI decreased by 80% (from 20.04 to 4.03) in 70 patients who completed the study. Mean symptom scores (all scales 0 to 4) decreased in patients with associated symptoms of: ♦ pruritus (n=79) from 2.04 to 0.27, ♦ joint pain (n=33) from 1.91 to 1.05, ♦ nail involvement (n=75) from 1.97 to 1.22.</td>
<td>No statistical analysis.</td>
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<tr>
<td>[20] Mrowietz Prospective open-label multi-centre</td>
<td>101 patients (67% men) with severe chronic plaque, guttate or exanthematic psoriasis. Baseline PASI at least 12. Mean age 43.4 years (range 21-69). Patients allowed to use salicylic acid (&lt;2%) or urea (&lt;10%) containing ointments.</td>
<td>16 weeks</td>
<td>AEs reported in 68 (67%) patients – 56% had GI symptoms and 31% flushing. Ten (10%) patients had leucopenia and 14 (14%) had eosinophilia. 31 patients withdrew from the study – 20 because of non-compliance (20%), seven (7%) because of AEs, two (2%) because of lack of efficacy and two (2%) for job reasons.</td>
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<td>[21] Fika Retrospective open-label single-centre</td>
<td>11 patients (45% men) with chronic plaque (73%) or guttate psoriasis who had not tolerated or failed to respond to other systemic agents (including methotrexate, ciclosporin, hydroxy-carbamide and acitretin) and/or phototherapy. Mean age 43 years (range 19-59).</td>
<td>Variable</td>
<td>Five (45%) patients considered completely clear of disease; four (36%) patients improved. Mean time to clearance was 5.5 months (range 4-9). AEs reported in all patients – 82% had GI symptoms and 18% flushing. 54% had lymphopenia and 27% transient eosinophilia. Three (27%) patients discontinued treatment, two because of AEs.</td>
<td>No statistical analysis. Assessment based on clinical examination alone.</td>
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<td>[22] Sladden Retrospective open-label single-centre</td>
<td>30 patients (70% men) with moderate or severe recalcitrant chronic plaque psoriasis who had not tolerated or failed to respond to at least two other second-line agents. Mean age 52 years (range 31-62).</td>
<td>Variable</td>
<td>15 (50%) patients clear or virtually clear, and some improvement seen in a further four (13%). Eight (27%) patients discontinued treatment due to GI AEs, two because of disease flare and one because of glomerulonephritis. 13 of the 19 patients continuing treatment had lymphopenia and two had microscopic haematuria (but continued Fumaderm®).</td>
<td>No statistical analysis. Assessment based on clinical examination alone.</td>
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<td>[23] Reich 2013a Prospective open-label multi-centre</td>
<td>195 patients (gender not reported) with moderate to severe psoriasis. 35% with hypertension, 30% dyslipidaemia, 11% inflammatory conditions, 10% diabetes, 8% coronary artery disease and 4% mental disorders. 66% had a BMI&gt;24 and 26% BMI&gt;30. 36% were smokers and 17% ex-smokers.</td>
<td>16 weeks</td>
<td>Mean reductions in PASI and DLQI scores were 43% and 40%, respectively. There was a trend towards a decreased clinical response in patients with vs. those without metabolic comorbidities (mean PASI reduction 39% vs. 54%; mean DLQI reduction 37% vs. 50%, respectively). 46 patients (20% of 230 patients in the safety dataset) reported at least one AE and 2% had a serious AE. More patients with metabolic comorbidities reported AEs than patients without (39 vs. 7, respectively). 32 patients (16% of 195 patients in the efficacy dataset) withdrew from the study, half due to AEs.</td>
<td>Published in abstract only. No statistical analysis. No details of baseline disease severity, previous or concurrent psoriasis treatments or AEs.</td>
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AEs = adverse events; BSA = body surface area; DLQI = Dermatology Life Quality Index; FAE = fumaric acid esters; GI = gastrointestinal; PASI = Psoriasis Area and Severity Index; PGA = Physician’ Global Assessment
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<td><strong>Short-term studies &lt; six months, continued (total n=537)</strong></td>
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<td>[24] Inzinger</td>
<td>Retrospective open-label single-centre</td>
<td>272 patients (gender not reported) with moderate to severe chronic plaque psoriasis identified from an electronic registry:  ♦ 200 received FAE. Mean baseline PASI score 11.6. Mean duration of disease 17.3 years. Mean age 40.4 years.  ♦ 72 received methotrexate (24 oral and 48 subcutaneous) increased to a maximum median dose of 20mg once weekly. Mean baseline PASI score 18.3. Mean duration of disease 16.7 years. Mean age 47.9 years. Most patients had previously received topical therapies but few had received systemic agents (proportions not reported).</td>
<td>12 weeks</td>
<td>In an intention-to-treat analysis, with significance level at p&lt;0.0125 (adjusted for multiple testing), there were no significant differences between groups in the proportion of patients achieving:  ♦ Complete remission - 6% on methotrexate and 1% on FAE (p=0.013),  ♦ PASI-90 response - 7% on methotrexate and 5% on FAE (p=0.762),  ♦ PASI-75 response - 24% on methotrexate and 27% on FAE (p=0.583), 32 (16%) patients on FAE did not respond and were given methotrexate - two (6%) patients achieved PASI-90 response and nine (28%) achieved PASI-75 response. Three (4%) patients on methotrexate did not respond and were given FAE - one achieved PASI-75 response, one did not respond and one discontinued FAE due to AEs.</td>
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<td><strong>Long-term studies &gt; six months (total n=2,092)</strong></td>
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<td>[6] Thio</td>
<td>Retrospective open-label multi-centre</td>
<td>Of 83 patients with chronic plaque psoriasis, 52 (56% men) were treated for at least six months (long-term users). Mean age 48 years. Concomitant topical therapy used by 29 (56%) patients; one also received phototherapy.</td>
<td>6 months (minimum)</td>
<td>26 (50%) long-term users were described as having very good improvement in their psoriasis and 15 (29%) had good improvement. Median percentage BSA affected was significantly reduced from baseline to final evaluation (p=0.0001).</td>
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<td>[25] Carboni</td>
<td>Prospective open-label single-centre</td>
<td>40 patients (63% men) with moderate to severe chronic plaque psoriasis, intolerant and/or resistant to other systemic agents. Mean baseline PASI score 26.5 (range 12-56). Median age 46.2 years (range 18-72).</td>
<td>6 months (minimum)</td>
<td>33 (82.5%) patients achieved complete clinical remission, eight after three months and 25 after six months. Mean PASI score at six months was 5.3 (CI not reported). Long-term follow up showed 20 (50%) patients continued therapy for 24 months without clinical evidence of recurrence; 40% interrupted treatment with Fumaderm® and showed recurrence at one to three months. Data were unavailable for four patients. 27% of patients had flushing, 20% abdominal pain, 15% pruritus and 10% diarrhoea. Four (10%) patients withdrew because of AEs.</td>
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**AEs** = adverse events; **BSA** = body surface area; **DLQI** = Dermatology Life Quality Index; **FAE** = fumaric acid esters; **GI** = gastrointestinal; **PASI** = Psoriasis Area and Severity Index; **PGA** = Physician’ Global Assessment

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<td>[5] Harries</td>
<td>Retrospective open-label single-centre</td>
<td>58 patients (57% men) with severe chronic plaque (94%), guttate (3%) or palmoplantar pustular (3%) psoriasis. 55 (95%) were intolerant or resistant to other systemic agents. Mean age 47.2 years (range 14-77). 21 (36%) initially concomitantly took a systemic agent (usually short-term).</td>
<td>Variable</td>
<td>Ten (17%) patients were clear or virtually clear and 22 (38%) showed some improvement. Mean time to clearance was 15.2 weeks. Seven patients had been on continuous treatment for over 12 months at the time of analysis. Two thirds had AEs – abdominal pain (61%), diarrhoea (55%) and flushing (45%). 57% had lymphopenia and 31% transient eosinophilia. 55% stopped treatment due to AEs (26%), lack of efficacy (21%), increased liver enzymes (5%), lymphopenia (2%).</td>
</tr>
<tr>
<td>[9] Brewer</td>
<td>Retrospective open-label single-centre</td>
<td>31 patients (68% men) with severe chronic plaque (93.5%) or palmoplantar pustular psoriasis, intolerant or resistant to other systemic agents. Mean age 46.8 years (range 27-78). Concomitant topical therapies were allowed; two patients additionally took hydroxyurea.</td>
<td>7.6 months (mean; range 0.5-18)</td>
<td>Ten (32%) patients were clear or had minimal residual psoriasis (complete responders - CR) and were still on treatment after a mean duration of 12.4 months. A further seven had good improvement. AEs occurred in 27 (87%) patients and led to treatment withdrawal in eight. They included flushing (68%), diarrhoea (61%) and abdominal pain (48%). 61% had lymphopenia, 32% eosinophilia and 13% increased liver enzymes.</td>
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<td>[26] Reich 2009</td>
<td>Retrospective multi-centre cross-sectional</td>
<td>984 patients (58% men) with mild to severe psoriasis (chronic plaque (87%), palmoplantar (3.5%) or generalised pustular (0.8%), guttate [16%], erythrodermic [2%]) or psoriatic arthritis (8.3%). Mean age 50.5 years (range 15-105). 21% had at least one medical condition (including cardiac, metabolic, musculoskeletal or vascular disease). 13.6% had previously taken other systemic agents.</td>
<td>2 years, or 3 years with no break &gt;6 months (minimum) 44 months (mean)</td>
<td>67% of patients markedly improved or were clear of psoriasis after six months (data available for 941 patients; 78% (n=901) after 24 months and 82% (n=566) after 36 months, according to PGA score. No difference in efficacy was reported between patients with or without co-morbidity. PASI scores were available for only 51 patients; after 36 months, mean PASI score fell by 79% from 22.7 to 4.8. Lymphopenia was reported in 41% of patients, raised liver enzymes in 13% and raised creatinine in 6%. 103 (10.5%) patients stopped taking Fumaderm® due to AEs.</td>
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<td>[27] Thaci 2012</td>
<td>Prospective open-label multi-centre</td>
<td>249 patients (gender not reported) with mild (1.4%), moderate (52.5%), severe or very severe (44.4%) plaque psoriasis newly started on FAE. Mean age 45.9 years.</td>
<td>12 months</td>
<td>Mean PASI score decreased from 16.9 to 6.8 (mean PASI reduction 60%). 52.4% of patients had a PASI-75 response. Mean DLQI score decreased from 11.8 to 1.8 (mean DLQI reduction 85%). Other outcomes included PGA and EuroQol 5 dimension (EQ-5D) – these data were not reported. 49 (20%) patients discontinued treatment, 11 (4.4%) due to an AE. No further detail on AEs or laboratory abnormalities reported.</td>
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<td>[28] Walker 2012</td>
<td>Prospective open-label multi-centre</td>
<td>249 patients (56% men) with mild (5%), moderate (34%), moderate-to-severe (44%), severe (16%) or very severe (1%) psoriasis. Mean age 49.7 years. Mean Fumaderm® dose 2.8 tablets (602mg) daily; &lt;30% of patients received 4-6 tablets daily.</td>
<td>12 months</td>
<td>Mean PASI score decreased from 16.8 to 5.6 (mean PASI reduction 67%). Mean DLQI score decreased from 10.5 to 3.3 (mean DLQI reduction 69%). Other outcomes included PGA and EuroQol 5 dimension (EQ-5D) – these were described as improved, but the data were not reported. No AE data reported.</td>
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<td>[29] Heelan 2014</td>
<td>Retrospective open-label single-centre</td>
<td>45 patients (62% men) with severe chronic plaque (93%), palmoplantar (4.5%) or nail (2%) psoriasis. Mean age 46 years (range 21-71). 31% previously used one or more systemic agents. 44% had received phototherapy.</td>
<td>10 months</td>
<td>32 (71%) patients showed significant improvement, with ten (22%) rated as clear. Of those receiving Fumaderm® first-line, 78% had significant improvement; 54% of those receiving Fumaderm® as second-line therapy had significant improvement. AEs reported in 66% of patients (28% of first-line patients and 38% of second-line patients) – 44% diarrhea, 40% abdominal cramps and 40% flushing. AEs led to discontinuation in 33% of patients. 24% had lymphopenia and 18% had eosinophilia, leading to treatment withdrawal in two patients. No statistical analysis. Assessment based on clinical examination alone.</td>
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<tr>
<td>[30] Burden-Teh 2013</td>
<td>Retrospective open-label single-centre</td>
<td>35 patients (51% men) with psoriasis. Mean age 54 years (range 23-75). 26 (74%) had failed two or more systemic agents.</td>
<td>8 months (maximum)</td>
<td>54% had an excellent response, 28% a partial response and 6% a poor response (data unavailable for three patients). 68% had GI AEs and/or flushing. 23% stopped treatment due to GI AEs, patient concerns over long-term treatment, or uncontrolled disease. 45% had laboratory abnormalities – most were transient but further details were not provided. Published in abstract only. No statistical analysis. Assessment based on clinical examination alone.</td>
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<td>[31] Thaci 2013</td>
<td>Retrospective open-label multi-centre cross-sectional</td>
<td>69 patients (75% men) with mild to very severe psoriasis. Mean age 57.8 years (range 25-84). All patients had at least one medical condition (including 64% metabolic disorder/obesity, 64% vascular disease, 20% cardiac disease). All patients were taking other medicines (including 48% drugs acting on the renin-angiotensin system, 42% lipid modifying drugs and 25% diabetes drugs).</td>
<td>27 months (mean) 6 weeks (minimum)</td>
<td>33% of patients markedly improved or were clear of psoriasis after three months (data available for 66 patients), 60.7% (n=61) after six months, 77% (n=53) after 12 months and 75% (n=40) after 24 months, according to PGA score. Clinically significant interactions reported between Fumaderm® and allopurinol (fulminant hepatitis resolved after both drugs stopped), and a beta-blocker (inadequate response to beta-blockade improved when Fumaderm® stopped). Lymphopenia was reported in 63% of patients at 12 months, and raised gamma-glutamyltransferase liver enzymes in 39% at three months. 22 (32%) patients stopped taking Fumaderm®, five (7%) because of an inadequate response, four (6%) because of AEs (including one case of lymphopenia) and one (1%) because of clinical improvement [reason not documented in 12 patients]. Incidence of AEs, other than laboratory abnormalities, not reported. No statistical analysis.</td>
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<td>[32] Walker 2014</td>
<td>Prospective open-label multi-centre</td>
<td>249 adults (56% men) with mild to very severe plaque psoriasis, already taking Fumaderm® before study baseline. Mean age 49.7 years (range 18-89). 41% of 246 patients had co-morbidities (21% hypertension and 5% diabetes). 35% took regular concomitant medicines, including 20% antihypertensives (types not specified). Mean daily Fumaderm® dose 2.8 tablets (602mg).</td>
<td>12 months</td>
<td>Mean PASI score decreased by 67% from 16.83 to 5.61. Mean PASI reduction was 14% in 10 patients with mild disease, 65% in 80 patients with moderate disease, 68% in 98 patients with moderate to severe disease, 67% in 38 patients with severe disease and 35% in two patients with very severe disease. Mean DLQI score decreased from 9.95 by 6%. Patients on antihypertensives had a lower mean reduction in PASI (37%). 104 patients discontinued the study. Among 76 patients, 43% stopped Fumaderm® because of AEs (mostly GI), 11% due to lack of efficacy and 4% because psoriasis completely cleared; 20% were lost to follow-up. Analysis was not by intention-to-treat. 78 patients (31.3%) received Fumaderm® for more than a month before baseline (mean 2.7 years). No data were reported on other psoriasis treatments.</td>
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</table>

AEs = adverse events; BSA = body surface area; DLQI = Dermatology Life Quality Index; FAE = fumaric acid esters; GI = gastrointestinal; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment
<table>
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<td><strong>Combination therapy studies (total n=470)</strong></td>
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<td>[33] Wain 2004</td>
<td>18 patients (83% men) with severe recalcitrant chronic plaque psoriasis who had previously taken at least two systemic agents. Age range 24-59 years. Five patients were also on ciclosporin, one was on acitretin and two were taking methotrexate.</td>
<td>12 weeks (minimum)</td>
<td>Mean change in PASI score was not significant (reduced by 1.5 ± 9.6 from a baseline mean PASI score of 15.0 ± 9). Five (28%) patients achieved at least a 50% reduction in PASI score, of whom two (11%) achieved at least a PASI-75 response. Mean DLQI score decreased by 1.7 ± 6 from 9.6 ± 6 (p&lt;0.5 – also non-significant). Three patients on ciclosporin were able to stop. 50% of patients had GI AEs and flushing. One patient had lymphopenia. Four patients discontinued due to lack of efficacy; none withdrew due to AEs.</td>
<td>Published in abstract only. PASI-50% is not considered an acceptable demonstration of treatment response [34].</td>
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<td>[34] Balasubramaniam</td>
<td>10 patients (70% men) with severe long-standing chronic plaque (90%) or erythrodermic psoriasis, intolerant or resistant to other topical and systemic therapies, and phototherapy. Mean age 48 years (range 32-65). All taking one or more systemic agents (acitretin, ciclosporin, hydroxyurea or methotrexate).</td>
<td>10 months (mean; range 3-19)</td>
<td>Psoriasis was considered improved in seven patients and well controlled in one patient (as assessed by their clinician), with two (20%) patients achieving complete clearance. The dose of at least one concomitant systemic agent was reduced in seven patients, although in two of these patients the dose of a second agent was increased. One patient had worsened disease but had stopped Fumaderm® because of overseas travel. 83% of patients had flushing and 58% had flatulence or diarrhoea. Two (11%) patients had raised creatinine. There was no evidence of any drug interactions or an increased rate of adverse effects due to combination therapy. One patient discontinued treatment due to flushing. [Data based on 12 patients including two on Fumaderm® monotherapy].</td>
<td>Fumaderm® dose increased every two weeks, rather than weekly. No statistical analysis. Assessment based on clinical examination alone.</td>
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<tr>
<td>[35] Wain 2010</td>
<td>80 patients (73% men) with severe recalcitrant chronic plaque psoriasis, 59% of whom were taking stable doses of one or two oral anti-psoriasis agents (only one patient had not previously received another systemic agent). Mean age 44 years (range 22-77).</td>
<td>3 months (minimum)</td>
<td>Mean PASI score decreased by 19% (from 13.9 ± 9.0 to 11.3 ± 9.2; p&lt;0.0001). Three (4%), six (8%) and 16 (20%) patients achieved a PASI-90, PASI-75 and PASI-50 response, respectively. Within three months, 19 of 53 concomitant oral anti-psoriasis agents were stopped and doses of a further 13 were reduced, without loss of disease control; by six months these had increased to 29 and 18, respectively (89% overall). In 74 patients, mean DLQI score fell from 11.2 ± 7.3 to 8.5 ± 7.4 at three months (p&lt;0.0001). 74% of patients had AEs (including diarrhoea, abdominal pain and flushing) and 36% stopped Fumaderm® because of them. Six (8%) patients developed hypertension requiring oral antihypertensives (all were on monotherapy at the onset of hypertension).</td>
<td>An intention-to-treat analysis was conducted. PASI-50% is not considered an acceptable demonstration of treatment response [34].</td>
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<td>[36] Reich 2013b</td>
<td>363 adults with moderate to severe psoriasis. Mean daily Fumaderm® dose 2.6 tablets (559mg). All patients received phototherapy (42% UVB) with mean duration of treatment 116 days.</td>
<td>12 months</td>
<td>Mean PASI decreased by 46% from 18.5 to 8.7 at three months, and to 5.1 at 12 months (mean PASI reduction 72%). 55% of patients achieved a PASI-75 response. Mean DLQI decreased by 66% from 12 at baseline to 3.4 at 12 months; 73% of patients achieved a DLQI reduction of at least 5 points. 27 patients (7%) had at least one AE; three (1%) had a serious AE.</td>
<td>Published in abstract only. No statistical analysis. No details of previous or concurrent systemic psoriasis treatments, or AEs provided.</td>
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### Studies involving children (total n=23)

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<td>[37] Gerdes</td>
<td>One 11-year old boy with severe chronic plaque psoriasis uncontrolled with topical therapies and UVB phototherapy. Given Fumaderm® 860mg daily for three months, reduced to a maintenance dose of 215-430mg daily. Concomitant topical therapies used for first two months.</td>
<td>3 years</td>
<td>PASI score decreased from 20.2 to 0.8 after three months. Body surface area involved decreased from 20% to 1%. Topical vitamin D analogues used intermittently for the head and groin. Psoriasis flared after three years but responded to a Fumaderm® dose increase to 860mg daily, plus topical corticosteroids. Patient had intermittent abdominal pain and flushing in the first three months. Lymphopenia was present throughout the three-year treatment period but remained above the threshold for drug discontinuation; all other laboratory results were normal.</td>
<td>Single case only. No statistical analysis. Laboratory tests were conducted every two months.</td>
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<td>[38] Balak</td>
<td>14 patients (50% boys) with chronic plaque psoriasis. Median age 15 years (range 8-17). Median disease duration 5 years (range 1-10). 93% received prior phototherapy and/or systemic agents. Median FAE maintenance dose 645mg. Concomitant use of topical therapies was allowed.</td>
<td>10 months (median; range 1-80). 7 patients treated ≥1 year</td>
<td>Five (36%) patients achieved complete clearance. One patient had an 82% reduction in PASI after four months, and three (21%) had a 69% reduction in PASI after six months. Five (36%) patients discontinued due to an inadequate clinical response. Five (36%) patients had abdominal pain, five (36%) had transient increases in liver enzymes or leucocytes, four (29%) had diarrhea and two (14%) had flushing. AEs led to treatment being stopped in two (14%) patients, one due to abdominal pain and the other due to flushing. One patient had a mild, transient raised creatinine, and another had mild proteinuria which lasted four weeks.</td>
<td>No statistical analysis. Patients received one of three Dutch FAE formulations, and were dosed as in adults. Assessment based on clinical examination.</td>
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<td>[39] Steinz</td>
<td>Six children (five girls) with moderate to severe plaque or guttae psoriasis refractory to topical treatment or UVB therapy. Median age 11.5 years (range 6-17). Maximum Fumaderm® dose 430mg (n=2) and 1,290mg (n=4). All received additional topical corticosteroids or vitamin D analogues; three received narrow-band UVB.</td>
<td>17.8 months (median; range 3-48).</td>
<td>33.3% of patients achieved a PASI 75 response, 16.7% PASI 90 and 50% PASI 100. Fumaderm was stopped after 12 weeks in one patient and another went into remission after nine months; in neither did psoriasis recur. AEs, mostly GI discomfort and flushing, occurred in two patients and were managed with slower dose increase or dose reduction. No patients discontinued because of AEs. 80% had fully reversible reduction in lymphocyte count. Proteinuria occurred in one patient, which responded to dose reduction from two to one tablet daily.</td>
<td>No statistical analysis. Laboratory tests were conducted monthly for four months, then every two months.</td>
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<td>[40] van Geel</td>
<td>Two non-English papers each describing a case study – a 14-year old patient with plaque psoriasis treated with FAE 430mg daily for at least 16 weeks, and a 15-year old patient with psoriasis (type not specified) treated with 860mg daily (maintenance 215-430mg daily) for 20 months.</td>
<td>Up to 20 months</td>
<td>PASI reduced from 19.7 to 1.0 in the 14-year old; the 15-year old achieved complete clearance. The 14-year old experienced reversible lymphopenia; the 15-year old had abdominal cramps.</td>
<td>Single cases only. No statistical analysis. Non-English papers so basic details obtained from a review article.</td>
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**AEs** = adverse events; **BSA** = body surface area; **DLQI** = Dermatology Life Quality Index; **FAE** = fumaric acid esters; **GI** = gastrointestinal; **PASI** = Psoriasis Area and Severity Index; **PGA** = Physician’ Global Assessment

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Q&A 246.4 Fumaderm®: what is the evidence for its efficacy and safety in treating psoriasis?

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