SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND

dimethyl fumarate 30mg and 120mg gastro-resistant tablets (Skilarence®)

SMC No 1313/18

Almirall Limited

9 March 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

dimethyl fumarate (Skilarence®) is accepted for restricted use within NHS Scotland.

Indication under review: for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.

SMC restriction: for use in patients in whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference.

In a 16 week, double-blind, phase III study, dimethyl fumarate was superior to placebo and non-inferior to a fumaric acid ester product at improving the symptoms of moderate to severe plaque psoriasis in adults.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.[1]

Dosing Information

To improve tolerability, it is recommended to begin treatment with a low initial dose with subsequent gradual increases. The starting dose of dimethyl fumarate is one 30mg tablet once daily increasing to a maximum of 720mg daily (as two 120mg tablets three times a day) over a period of at least nine weeks. If a particular dose increase is not tolerated, it may be temporarily reduced to the last tolerated dose. If treatment success is observed before the maximum dose is reached, no further increase of dose is necessary. After clinically relevant improvement of the skin lesions has been achieved, consideration should be given to gradual reduction of the daily dose to the maintenance dose required by the individual.

For further detail, please see the summary of product characteristics.

Dimethyl fumarate is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.[1]

Product availability date

12 September 2017

Summary of evidence on comparative efficacy

The mechanism of action of dimethyl fumarate is not completely understood. Dimethyl fumarate and its metabolite monomethyl fumarate are thought to act on multiple intracellular pathways producing anti-oxidant, anti-inflammatory and immunomodulatory effects. These actions result from a shift in helper T cell phenotype, a reduction in cytokine production and inflammatory infiltrate in psoriatic plaques and inhibition of keratinocyte proliferation.[1 2]

The submitting company has requested that SMC considers this product when positioned for use in the treatment of moderate to severe psoriasis in patients in whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference.

The pivotal study, BRIDGE, was a multicentre, double-blind, active and placebo controlled phase III study in patients with chronic plaque psoriasis. A total of 704 patients were randomised in a 2:2:1 ratio to oral dimethyl fumarate, Fumaderm® (fumaric acid esters) or placebo respectively for a 16 week treatment phase, with up to 12 months follow-up off-treatment to assess safety, persistence of effect and disease rebound. Patients were aged 18 years or older with a diagnosis of chronic plaque psoriasis for at least 12 months before enrolment; had moderate to severe psoriasis defined in terms of the following criteria: psoriasis area and severity index (PASI) score >10 (scale of 0 to 72), body surface area (BSA) affected by psoriasis >10% and physician's global assessment (PGA) moderate to severe (score of 3=moderate, 4=moderate to severe; or 5=severe on a scale of zero to five); had received prior therapy with at least one systemic drug for psoriasis that was discontinued e.g. due to an adverse event or insufficient effect, or were naïve to systemic treatment but identified as a candidate for systemic treatment.[2 3 4]

Treatment with dimethyl fumarate, Fumaderm® or matching placebo was up-titrated over the first nine weeks, from 30mg daily in week one to a maximum daily total of 720mg in week nine if tolerated, and if required for efficacy. Dimethyl fumarate and Fumaderm® were considered equivalent. Both contain the same amount of dimethyl fumarate but Fumaderm® includes additional monoethyl fumarate salts. Tablets of each of the active treatments, and matching placebo were available in 30mg and 120mg dimethyl fumarate strengths. The 720mg daily dose, or maximum tolerated dose if unable to take 720mg daily, or dose at which treatment success was achieved if this was before week nine, was continued from week 10 to 16. Daily doses of 30mg and 120mg were taken once daily, daily doses of 60mg and 240mg were taken as two divided doses and doses of 90mg or at least 360mg were taken as three divided doses.[2]

The co-primary outcomes were achievement of PASI 75 response (75% reduction in PASI score from baseline) and PGA scores of 0 'clear' or 1 'almost clear' following 16 weeks of treatment. The analysis was conducted in the full analysis set which included all patients that had been randomised, with at least one dose of study medication and at least one measurement of PASI 75 and PGA. The comparative results of the co-primary outcomes are presented below in table 1. The proportions of responders in the dimethyl fumarate (n=267), Fumaderm® (n=273) and placebo (n=131) groups respectively for PASI 75 were; 37%, 40% and 15%, and for PGA score 0 (clear) or 1 (almost clear) were; 33%, 37% and 13%.[1 2 3 4]

Table 1. Comparative risk differences of co-primary outcome responders in full analysis set at week 16.[1 2 3]

	PASI 75 versus placebo	**PASI 75 versus Fumaderm®**	**PGA score 0 or 1 versus placebo**
Dimethyl fumarate, RD in FAS, % difference (99.24% CI)	22.2 (10.7 to 33.7) p<0.0001 superior	-2.8 (-14.0 to 8.4) p=0.0003 non-inferior [a]	20.0 (9.0 to 31.0) p<0.0001 superior

[a]non-inferiority test based on a 15% margin of non-clinical relevance and required a p-value <0.0038 to be statistically significant.
PASI=psoriasis area and severity index, PGA=physician's global assessment, RD=risk difference, FAS=full analysis set, CI=confidence interval.

The following are key secondary outcome results from the BRIDGE study;

- There was a numerical advantage favouring dimethyl fumarate and Fumaderm® over placebo in terms of PASI 75 and PGA score of 'clear' or 'almost clear' responders after 8 weeks of treatment, but this was not statistically significant
- There was a statistically significant improvement when dimethyl fumarate was compared with placebo after 16 weeks of treatment in terms of mean change from baseline BSA affected, PASI 50 and PASI 90 responders

The Dermatology Life Quality Index (DLQI) questionnaire measures how much a skin problem has affected a patient's life over the last week (range 0 to 30, with scores of 0 to 1 indicating no effect on patient's life, 2 to 5 indicating a small effect on patient's life, 6 to 10 indicating a moderate effect on patient's life, 11 to 20 indicating a very large effect on patient's life and of 21 to 30 an extremely large effect on patient's life). Dimethyl fumarate was associated with a statistically significant improvement in DLQI score over placebo, with mean scores in both arms improved from baseline at week 16 (mean score in the dimethyl fumarate arm improved from 11.3 at baseline to 5.4 at week 16) and there was no statistical difference when dimethyl fumarate was compared with Fumaderm®.[2 3 6]

At two months following the final dose of study medication, loss of treatment effect and rebound effects were lower in the dimethyl fumarate and Fumaderm® groups than in the placebo group but only 16% (110/671) of patients that entered the BRIDGE study completed the extension phase and these results should be interpreted with caution.[3]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

During the treatment phase of the BRIDGE study, treatment emergent adverse events (TEAE) occurred in 84% (234/279), 84% (238/283) and 60% (82/137) of patients in the dimethyl fumarate, Fumaderm® and placebo groups and they led to study discontinuation in 24%, 24% and 5.8% of patients respectively. TEAEs considered to be related to study treatment occurred in 74% (206/279), 74% (209/283) and 40% (54/137) of the respective groups. Serious TEAEs were reported in 3.2%, 2.8% and 3.6% of patients in the treatment groups listed respectively. Investigators considered that only four of these were treatment related, all occurred in patients treated with Fumaderm® and all were gastrointestinal in nature.[2 3]

In the dimethyl fumarate, Fumaderm® and placebo groups respectively, the following adverse events occured: diarrhoea (39%, 40% and 17%), abdominal pain (20%, 16% and 5%), nausea (11%, 8% and 4%), vomiting (5%, 7% and 1%), erythema (10%, 8% and 2%), flushing (18%, 16% and 1%), lymphopenia (10%, 10% and 0%), and eosinophilia (9%, 6% and 0%).[2]

Summary of clinical effectiveness issues

Psoriasis is a chronic, immune-mediated, inflammatory condition of the skin with a relapsing-remitting clinical course. Plaque psoriasis is the most common type and is characterised by red, scaly patches, plaques and pustules that usually itch. The main types of treatment for psoriasis include topical therapy (such as corticosteroids and vitamin D analogues), phototherapy and systemic non-biological therapy with conventional agents (e.g. methotrexate, ciclosporin, acitretin) or non-conventional agents (apremilast, fumaric acid esters – unlicensed) or biological therapy with agents such as tumour necrosis factor (TNF) antagonists, anti-interleukin (IL)-12/IL-23 and anti-IL-17A agents.[7 8]

Fumaderm® is a combination of fumaric acid esters, including dimethyl fumarate and is licensed for the treatment of moderate to severe plaque psoriasis in Germany. It is currently available and prescribed as an unlicensed medicine in Scotland and can be considered as an alternative maintenance therapy for patients who are not suitable for other systemic therapies or have failed other therapies according to the Scottish Intercollegiate Guidelines Network (SIGN), clinical guideline 121 (2010); Diagnosis and management of psoriasis and psoriatic arthritis in adults.[2 7] Apremilast was accepted for use in NHS Scotland in June 2015 (SMC 1052/15) for a similar patient group. Many biologic therapies have been accepted for use in NHS Scotland in moderate to severe psoriasis. Fumaric acid esters are considered a non-biologic systemic treatment option which may avoid the need for treatment with a biologic therapy in those achieving treatment success.

The submitting company has requested that SMC considers dimethyl fumarate when positioned for use in patients in whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference. Approximately 74% of patients in the BRIDGE study were systemic treatment naïve and at least 45% of patients were systemic therapy and phototherapy naïve.[2]

The BRIDGE study showed dimethyl fumarate is superior to placebo for achieving the co-primary endpoints of PASI 75 and PGA score of 0 (clear) or 1 (almost clear) response after 16 weeks of treatment in patients with moderate to severe psoriasis in line with the European Medicines Agency (EMA) guideline on clinical investigations of medicinal products indicated for the treatment of psoriasis. Dimethyl fumarate was also shown to be non-inferior to Fumaderm® in terms of achieving PASI 75 response.[2 3] A subgroup of the BRIDGE study represents part of the proposed positioning. The duration of the pivotal study was 16 weeks, in line with the EMA guideline for clinical studies in patients with psoriasis, but nine weeks may be required for titration to the optimal dose of dimethyl fumarate and previous studies with Fumaderm® showed maximum efficacy can take up to 12 months. There is a lack of long-term data on treatment with dimethyl fumarate and seasonal variation of psoriasis may not have been accounted for by the 16 week treatment phase, however the EMA states that the results of the BRIDGE study support extrapolation to longer term Fumaderm® data.[3 4]

Discontinuation rates in the BRIDGE study for patients treated with both dimethyl fumarate and Fumaderm® were relatively high in comparison to the placebo group (dropout rates of 37%, 37% and 29% respectively). The power calculation for the BRIDGE study was based on reported differences between Fumaderm® and placebo, estimated as a PASI 75 difference of 40% between dimethyl fumarate and placebo but the BRIDGE study only showed a difference of 22.5%. The non-inferiority margin was set at 15%. The EMA advises that, given the observed effect size, strict non-inferiority cannot be concluded but that adequate comparability is supported by the equal quantity of dimethyl fumarate in both Fumaderm® and dimethyl fumarate, similar bioavailability, and the comparable efficacy and safety results from the BRIDGE study.[2 3]

Baseline data on the duration of disease for patients in the BRIDGE study were not recorded as per EMA guidance for clinical studies in patients with psoriasis. Imbalances in baseline characteristics in the subgroup analysis of patients with prior systemic treatment may have biased the results.[4 5] Randomisation was not stratified by centre, and results were not adjusted for centre.[3]

There are no direct comparative data for dimethyl fumarate versus apremilast. The submitting company presented a Bayesian network meta-analysis (NMA) of six studies using fixed effects to compare the efficacy of dimethyl fumarate to apremilast via placebo as the common comparator. Initially the NMA results were presented as PASI response (pooled multinomial of PASI 50, 75 and 90) with reference to placebo. In response to a request, the company provided results in terms of relative risk of PASI 75 response. The primary outcome reported was PASI 75. PASI 50 (50% reduction in PASI score from baseline) and PASI 90 (90% reduction in PASI score from baseline) were also reported. Apremilast had a higher probability of achieving a PASI 75 response than dimethyl fumarate in both the full population and in the subgroup with prior systemic non-biologic or phototherapy treatment. The credible intervals in the subgroup analysis were wider than in the base case analysis and patient numbers in the dimethyl fumarate subgroup were small. Limitations of the NMA include heterogeneity between the dimethyl fumarate study and the five apremilast studies: smaller proportion of patients in the BRIDGE study had severe disease compared with the apremilast studies and differing placebo responses across the studies. There was a lack of transparency in the NMA regarding prior treatments and different patient subgroups were presented in the clinical efficacy section and indirect treatment comparison. The NMA subgroup includes some patients with prior phototherapy only, who are not explicitly accounted for in the positioning statement.

Rare but serious events including serious opportunistic infections such as progressive multifocal leukoencephalopathy and malignancies have been reported with fumaric acid esters, and the EMA has requested a post-authorisation safety study to gather more information on these risks.[3]

The beneficial effects of dimethyl fumarate gain statistical significance over placebo after between 8 and 16 weeks of treatment. Patients may experience adverse effects for the first 8 weeks of treatment without any benefit. The summary of product characteristics (SPC) for dimethyl fumarate advises monitoring of

liver function, renal function and full blood count prior to starting treatment and then every three months, with more frequent monitoring if there are aberrant results. British Association of Dermatologists (BAD) recommend that treatment with fumaric acid esters should stop after six months if there has not been a considerable improvement.[1 9 10] There is no direct evidence supporting maintenance of effect when patients are switched from Fumaderm® to dimethyl fumarate.

Clinical experts consulted by SMC considered that dimethyl fumarate is an advancement in terms of having a licensed fumaric acid ester product available and would be considered for use when other systemic non-biologic therapies such as methotrexate, ciclosporin and acitretin have failed or are not appropriate due to intolerance or contraindication and before biologic therapies.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis which compared dimethyl fumarate against apremilast in adult patients with moderate to severe plaque psoriasis for whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference. A sensitivity analysis was also presented versus Fumaderm®.

A Markov state transition model was used and consisted of a trial period and a maintenance period for each treatment option. The trial phase of the model consisted of a 16 weeks treatment period and patients could move to the maintenance phase if they achieved a response, defined as a PASI 75 response, at 16 weeks. Responders were assumed to continue treatment indefinitely (i.e. there was no fixed treatment duration) however patients could withdraw from treatment in the maintenance phase and receive best supportive care (BSC). Patients who did not achieve a response at 16 weeks discontinued treatment and also received BSC. A time horizon of 10 years was used in the base case analysis.

It is worth noting that by withdrawing patients from treatment at 16 weeks, if they have not achieved a response, a stopping rule has been applied to the economic model.

Clinical data were mainly taken from a NMA which generated PASI responses at 16 weeks for dimethyl fumarate and apremilast. The annual withdrawal rate for patients who entered the maintenance phase was taken from published sources and informed by Scottish clinicians consulted by the company. An annual withdrawal rate of 20% was used in the base case analysis and applied to both arms of the model. Mortality was based on age- specific general mortality estimates.

Utility values were taken from published sources and the following values were used in the analysis, baseline utility: 0.70, PASI response <50: 0.75, PASI response ≥50-<75: 0.87, PASI response ≥75-<90: 0.89, and PASI response ≥90: 0.91. Disutilities related to adverse events were not included in the model.

Medicine costs were included in the analysis as well as the cost of monitoring, outpatient visits, non-responder and BSC costs.

The base case results indicated that dimethyl fumarate was less expensive than apremilast with savings of £6,772 over the model time horizon and also less effective with a reduction in quality adjusted life-years (QALYs) of 0.04. The submitting company presented the incremental cost-effectiveness ratio (ICER) in terms of apremilast versus dimethyl fumarate and reported the ICER as £166,841. The submitting company noted that as the ICER was relatively large, apremilast would not be considered cost-effective and therefore dimethyl fumarate would be the cost-effective treatment option. However, an alternative interpretation of the result is that dimethyl fumarate was less costly and less effective

when compared to apremilast and dimethyl fumarate would be considered cost-effective as the savings are relatively large when compared against the QALYs lost.

The results of selected sensitivity analysis versus apremilast are presented below.

Table 3. Selected sensitivity analyses versus apremilast

	Analysis	ICER
1	Cost of dimethyl fumarate increased to £5.92 per tablet	£29,760
2	30% withdrawal dimethyl fumarate	£91,578
3	10% withdrawal apremilast	£81,008
4	Utility in BSC health state rebounds to baseline value (0.70)	£99,193
5	Increase the cost of BSC	£115,535

It should be noted that Fumaderm® is available as an unlicensed treatment in the UK and the company provided analyses upon request versus Fumaderm® which included an estimate of the price of Fumaderm®. However owing to the commercial in confidence issues relating to the Fumaderm® cost, it is not possible to present results versus Fumaderm®.

The main weaknesses were

- The economic model used response rates for placebo from the NMA to model the efficacy of BSC; therefore patients who transitioned to BSC could attain utility levels associated with PASI response ≥50-<75, ≥75-<90, and ≥90. In addition, patients treated with BSC who did not achieve a PASI response of above 50 were attributed a utility of 0.75 as opposed to the baseline value of 0.70. The submitting company provided a sensitivity analysis which removed the response- based utilities from the BSC health state and all BSC patients were assigned a utility of 0.70. The results are available in Table 3 scenario 4 above and indicated that dimethyl fumarate remained cost-effective in this scenario.
- There is a lack of long term data to inform the economic analysis and the economic model used the same withdrawal rate in the maintenance phase despite the NMA suggesting that apremilast was more effective than dimethyl fumarate. The company presented sensitivity analyses which changed the withdrawal rates used in the economic model. The sensitivity analyses indicated that dimethyl fumarate remained the cost-effective treatment option (see Table 3 above, scenarios 2 and 3).
- The base case result is presented against apremilast although Fumaderm® may be considered the more relevant comparator. As noted above, analyses were provided versus Fumaderm® upon request. These analyses cannot be presented owing to the commercial in confidence issues relating to the Fumaderm® cost.

Despite the above uncertainties the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from the Psoriasis Association and the Psoriasis and Psoriatic Arthritis Alliance (PAPAA), both are registered charities.
- The Psoriasis Association has received 4.09% pharmaceutical company funding in the past two years, with none from the submitting company. PAPAA has not received any pharmaceutical company funding in the past two years.
- Psoriasis is a lifelong, visible condition which can occur at any age. It can be a debilitating disease that impacts all aspects of life, physically and psychologically. Owing to the highly visible nature of psoriasis, patients often avoid social situations and it can affect career choice. It can also have a significant impact on the wider family and on personal relationships.
- Patients with moderate to severe psoriasis have usually been through a long journey of treatment trial and error. There is a significant administration burden from current treatments such as topical treatments and light therapy. Patients report spending on average approximately two hours a day applying topical treatments. Light therapy requires regular visits to a specialist centre for a number of days per week for a number of weeks per year which can be difficult for people who work.
- Dimethyl fumarate is an oral treatment which is preferred by most patients compared with other administration methods. Although the gastro-intestinal side-effects may be problematic for some people, patients would welcome an additional treatment option. A new oral treatment gives hope for people with psoriasis.

Additional information: guidelines and protocols

The SIGN guideline on Diagnosis and management of psoriasis and psoriatic arthritis in adults (guideline 121) was published in 2010. This recommends that patients with psoriasis are initially treated with topical therapies such as topical corticosteroids and vitamin D analogues. Patients not responding to topical therapy should be referred to a dermatologist and considered for phototherapy. Patients with refractory or severe psoriasis should be considered for treatment with a conventional systemic therapy such as methotrexate, ciclosporin or acitretin with choice based on the risks and benefits of the individual treatments. If the aforementioned treatments fail, are contraindicated or are not tolerated, biologic agents should be considered. The guideline states that fumaric acid esters can be considered an alternative maintenance therapy for patients who are not suitable for other systemic therapies such as methotrexate, ciclosporin and acitretin or have failed to get a response on these treatments. These guidelines pre-date the introduction of apremilast.[7]

The National Institute for Health and Care Excellence (NICE) published a clinical guideline (CG 153) on the assessment and management of psoriasis in 2012. The recommendations in this guideline are generally in line with SIGN 121. Fumaric acid esters are not mentioned in this guideline but apremilast is listed as an alternative systemic non-biological therapy.[8]

The European S3-Guidelines on the systemic treatment of psoriasis vulgaris – update 2015, recommend the use of fumaric acid esters: for induction treatment, long term treatment and slow increase dosing regimen. Apremilast was granted market authorisation after the cut-off for inclusion in this guideline.[9]

Additional information: comparators

Apremilast, Fumaderm® (unlicensed fumaric acid esters)

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Dimethyl fumarate	**Range 240mg to 720mg in divided doses daily* maintenance therapy (following induction)**	**1,543 to 4,630**
Apremilast	30mg orally twice daily as maintenance therapy (following induction)	7150

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS on 7 December 2017. *the dose of dimethyl fumarate may be titrated up and down depending on tolerance and benefit derived. There is no published UK cost for Fumaderm®.*

Additional information: budget impact

The submitting company estimated there would be 15,712 patients eligible for treatment with dimethyl fumarate in all years to which confidential estimates of treatment uptake were applied.

The gross impact on the medicines budget was estimated to be £639k in year 1 rising to £3.51m in year 5. As other medicines are expected to be displaced the net medicines budget impact is expected to be a saving of £1.16m in year 1 rising to a saving of £6.37m in year 5.

References

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This assessment is based on data submitted by the applicant company up to and including 14 February 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.