Dimethyl fumarate for plaque psoriasis

SUMMARY

Dimethyl fumarate is intended to be used for the treatment of moderate to severe plaque psoriasis. If licensed dimethyl fumarate may present an additional treatment option for this patient group, potentially delaying or avoiding the need for biological therapies. Dimethyl fumarate is one of three fumaric acid salts present in Fumaderm, a drug already licensed in Germany for plaque psoriasis.

Plaque psoriasis is the most common type of psoriasis, representing 90% of cases. The estimated UK prevalence of psoriasis is 1.5-1.63%, with 1.1% of suffering with severe disease. It has a bimodal onset, with the first peak occurring in persons aged 16 to 22 years, and the second in persons aged 57 to 60 years. The prevalence of psoriasis in those younger than 10 years is estimated to be 0.55% and 1.4% in those aged between 10 and 19 years. The estimated prevalence of people currently eligible for biological therapy in England is 1.1% of those with psoriasis. Chronic plaque psoriasis is typified by itchy, well demarcated circular-to-oval bright red/pink elevated lesions (plaques) with overlying white or silvery scale, distributed symmetrically over extensor body surfaces and the scalp. Current treatment options include topical ointments and emollients, phototherapy, systemic therapies (e.g. oral retinoids) and biological therapies.

Dimethyl fumarate is currently in a phase III clinical trial comparing its effect on psoriasis area and severity index (PASI) against treatment with Fumaderm or placebo. This trial is expected to complete in December 2014.
TARGET GROUP

- Plaque psoriasis: moderate to severe.

TECHNOLOGY

DESCRIPTION

Dimethyl fumarate (LAS-41008) is a methyl ester of fumaric acid. Fumaric acid and its sodium salts have been previously used in psoriasis, and dimethyl fumarate appears to be the most active compound when given orally. Dimethyl fumarate inhibits certain functions of endothelial cells, namely, differentiation, proliferation and migration, as well as affecting the immune system and proliferating cells in general. Dimethyl fumarate is administered at a starting dose of 30mg daily, titrated up to a maximum of 720mg daily.

Dimethyl fumarate is also in development for multiple sclerosis. It is also one of three fumaric acid salts present in Fumaderm, which is currently licensed for the treatment of plaque psoriasis in Germany.

INNOVATION and/or ADVANTAGES

If licensed dimethyl fumarate may present an additional treatment option for this patient group, potentially delaying or avoiding the need for biological therapies.

DEVELOPER

Almirall SA.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Psoriasis is defined as a chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations. It is characterised by scaly skin lesions, which can be in the form of patches, papules, or plaques. The skin lesions of psoriasis are characterised by:
- Hyperproliferation of the epidermis.
- Dilation and proliferation of blood vessels in the dermis.
- Accumulation of inflammatory cells, particularly neutrophils and T-lymphocytes.

Chronic plaque psoriasis is typified by itchy, well demarcated circular-to-oval bright red/pink elevated lesions (plaques) with overlying white or silvery scale, distributed symmetrically over extensor body surfaces and the scalp. Plaque psoriasis may manifest differently in children – plaques may not be as thick, and the lesions may be less scaly. Psoriasis may also appear in the flexural areas in children and the disease more commonly affects the face compared with adults.
None identified.

**CLINICAL NEED and BURDEN OF DISEASE**

Plaque psoriasis is the most common type of psoriasis, representing 90% of cases. The estimated UK prevalence of psoriasis is 1.5-1.63%\(^4,5\), with 1.1% of people suffering with severe disease\(^5\). It has a bimodal onset, with the first peak occurring in persons aged 16 to 22 years, and the second in persons aged 57 to 60 years. The prevalence of psoriasis in those younger than 10 years is estimated to be 0.55% and 1.4% in those aged between 10 and 19 years\(^4,6\). The estimated prevalence of people currently eligible for biological therapy in England is 1.1% of those with psoriasis\(^5\). Females typically develop plaque psoriasis earlier than males, and patients with a positive family history for psoriasis also tend to have an earlier age of onset\(^4\). Acute flares or relapses of plaque psoriasis may evolve into more severe disease, such as pustular or erythrodermic psoriasis\(^7\). The significant reduction in quality of life and psychosocial disability suffered by people with psoriasis underlies the need for prompt, effective treatment, and long-term disease control\(^8\).

In 2011-12, for all age groups there were 13,546 hospital admissions due to psoriasis in England, equating to 14,094 finished consultant episodes and 23,195 bed days. There were a total of 356 finished consultant episodes for patients aged up to 14 years in 2011-12\(^9\).

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal. Ustekinumab for the treatment of adults with moderate to severe psoriasis (TA180). September 2009\(^10\).
- NICE technology appraisal. Infliximab for the treatment of adults with psoriasis (TA134). January 2008\(^12\).
- NICE technology appraisal. Etanercept and efalizumab for the treatment of adults with psoriasis (TA103). July 2006\(^13\).

**Other Guidance**

- SIGN. Diagnosis and management of psoriasis and psoriatic arthritis in adults. 2010\(^16\).
- British Association of Dermatologists and Primary Care Dermatology Society. Clinical guideline: Recommendations for the initial management of psoriasis. 2009\(^17\).
EXISTING COMPARATORS and TREATMENTS

Current treatment options for plaque psoriasis include\(^{15,18,21,22}\).

**Topical (alone or in combination)**

- Emollients.
  - Corticosteroids: betamethasone dipropionate.
  - Vitamin D analogues: calcipotriol, calcitriol, tacalcitol and tazarotene (with or without phototherapy).
  - Tars (with or without phototherapy).
  - Dithranol (with or without phototherapy).
  - Retinoids: tazarotene.
  - Salicylic acid.
  - Tacrolimus ointment (not licensed for this indication).

- Phototherapy
  - Narrow band UVB and psoralen and UVA combination (PUVA).

**Systemic therapies (for the treatment of patients with severe or refractory psoriasis)**

- Oral retinoids: acitretin (with or without phototherapy).
- Hydroxycarbamide (not licensed for this indication).
- Fumaric acid esters: monoethylfumarate and dimethylfumarate (licensed in the EU but not in the UK).
- Ciclosporin.
- Methotrexate.

**Biologics (for the treatment of patients intolerant, contraindicated or refractory to other treatments)**

Drugs affecting the immune response: adalimumab, etanercept, infliximab, and ustekinumab.

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**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01726933, M41008-1102, 2012-000055-13; dimethyl fumarate or Fumaderm vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Almirall SA.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^{23}).</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not incl UK).</td>
</tr>
</tbody>
</table>
Design | Randomised, placebo-controlled.
Participants | n=690 (planned); ≥18 years; moderate to severe plaque psoriasis.
Schedule | Randomised to oral dimethyl fumarate, at a starting dose of 30mg daily, titrated up to a maximum of 720mg daily, Fumaderm (dose not reported) or placebo.
Follow-up | Active treatment period 6 weeks, follow-up 12 months thereafter.
Primary outcome/s | Psoriasis area and severity index (PASI) 75; physician global assessment (PGA).
Secondary outcome/s | Body surface area; dermatological life quality index; PASI 75 at week 3, 8 and follow-up; PGA at week 3, 8 and follow-up; adverse events.
Expected reporting date | Estimated study completion date Dec 2014.

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**ESTIMATED COST and IMPACT**

**COST**

The cost of dimethyl fumarate is not yet known. The costs of other selected treatments for severe plaque psoriasis are given below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit Cost</th>
<th>Annual cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>80mg SC; then 40mg SC on alternate weeks one week after initial dose.</td>
<td>£352 (40mg, prefilled syringe)</td>
<td>£9,504</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>25mg SC twice weekly or 50mg SC once weekly.</td>
<td>£89 (25mg, prefilled syringe)</td>
<td>£9,256</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>5mg/kg IV repeated at 2 and 6 weeks; then every 8 weeks.</td>
<td>£420 (100mg vial)</td>
<td>£11,760</td>
</tr>
<tr>
<td>Ustekinumab (Stelara)</td>
<td>Initially 45mg, then 45mg 4 weeks after initial dose, then 45mg every 12 weeks.</td>
<td>£2147 (45mg, prefilled syringe)</td>
<td>£10,735</td>
</tr>
</tbody>
</table>

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival | ☑ Reduced symptoms or disability
- Other | ☐ No impact identified

**Impact on Services**

- Increased use of existing services | ☑ Decreased use of existing services: oral treatment option. Fumaderm is also currently used off-licence in most UK departments to control chronic plaque psoriasis. This may negate the need for specialist training in order to initiate and prescribe this therapy.
- Re-organisation of existing services | ☑ Need for new services
- Other | ☐ None identified

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*a* Based on an average body weight of 77.9kg.

*b* Expert personal communication.
Impact on Costs

☐ Increased drug treatment costs
☐ Other increase in costs
☑ Other: uncertain unit cost compared to existing treatments.
☐ Reduced drug treatment costs
☐ Other reduction in costs
☐ None identified

Other Issues

☑ Clinical uncertainty or other research question identified: Expert opinion suggests it would be beneficial to have more data on the efficacy of dimethyl fumarate in a paediatric population and to determine how immunosuppressive the therapy is in relation to other systemic agents for plaque psoriasis (e.g. methotrexate). There are also a number of other oral drugs in development for plaque psoriasis.
☐ None identified

REFERENCES


c Expert personal communication.