Dimethyl fumarate (Skilarence®) for the treatment of plaque psoriasis in adults

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 9 May 2018

Zorginstituut Nederland has carried out an assessment of the medicinal product dimethyl fumarate (Skilarence®), whereby they came to the following conclusion.

In a letter dated 13 February 2018 (CIBG-18-05820), the Minister of Health, Welfare and Sport (WVS) asked the *Zorginstituut* to carry out an assessment of whether dimethyl fumarate (Skilarence®) is interchangeable with a medicinal product that is already included in the Medicine Reimbursement System (GVS). The *Zorginstituut* has completed its assessment.

Dimethyl fumarate (Skilarence®) is registered for the treatment of moderate to severe plaque psoriasis in adults in need of systemic drug therapy. Skilarence® is available as 30 mg and 120 mg gastro-resistant tablets. To improve tolerance, it is recommended to start treatment with a low dose of 30 mg once daily and to subsequently increase the dose gradually over 9 weeks. If successful treatment is observed before reaching the maximum dose, no further dose increase is needed. The maximum daily dose permitted is 720 mg (3 x 2 tablets dimethyl fumarate 120 mg).

Background

Fumarates have been used for decades for the treatment of moderate to severe plaque psoriasis and they are recommended in current Dutch guidelines. Until recently, no registered fumarate was available for this indication in the Netherlands and psoriasis was treated with pharmacy preparations, namely dimethyl fumarate (DMF) alone, or a combined preparation comprised of dimethyl and monoethyl fumarate (MEF). Skilarence® is the first registered dimethyl fumarate for this indication.
Dimethyl fumarate is already included in the GVS on List 1A of the Health Insurance Regulation (Rzv) for the indication multiple sclerosis. List 2 conditions are attached to the reimbursement of dimethyl fumarate. From a technical perspective, this assessment is an extension of the detailed conditions for the reimbursement of dimethyl fumarate.

GVS assessment

The manufacturer of dimethyl fumarate (Skilarence®) has applied for placement on List 1A in the existing cluster together with Tecfidera®. Tecfidera®, which has the same active substance as Skilarence®, namely dimethyl fumarate, is registered for the indication relapsing remitting multiple sclerosis.

Conclusion regarding interchangeability

The GVS report concludes that, based on the criteria for interchangeability, dimethyl fumarate (Skilarence®) is interchangeable with another medicinal product in the GVS that has the same active substance, namely Tecfidera®. Tecfidera® is included in the GVS on List 1A in cluster 0N07XXCO, together with teriflunomide (Aubagio®) tablet (coated) 14 mg.

Tecfidera® is currently clustered with medicines for relapsing remitting multiple sclerosis (RRMS). In view of the higher prevalence of the psoriasis indication in comparison with RRMS, the inclusion of Skilarence® in the GVS means plaque

psoriasis will become the most important indication for dimethyl fumarate. Teriflunomide (Aubagio®) is only registered for RRMS and it has not been indicated nor studied for use on plaque psoriasis. This means that teriflunomide is no longer interchangeable with dimethyl fumarate, due to a difference in therapeutic area.

Standard dose
The WHO fixed the DDD of dimethyl fumarate at 480 mg. This DDD falls within the dose range mentioned in the registration text of both Skilarence® and Tecfidera®. The standard dose for Skilarence® can thus be fixed at 480 mg.

Budget impact analysis
The budget impact analysis looked at the added costs involved in extending the specific condition for dimethyl fumarate on List 1A of the GVS to include the treatment of moderate to severe plaque psoriasis in adults in need of systemic drug therapy. The conclusion is that, taking into account the assumptions in the budget impact analysis, extending the specific condition for dimethyl fumarate with plaque psoriasis will be accompanied by additional costs to the pharmacy budget of €6.51 million to €7.94 million in the third year, whereby Skilarence® will substitute the existing pharmacy preparations.

Considerations of *Zorginstituut Nederland*
The budget impact analysis shows that Skilarence® will be approximately twice as expensive as the existing pharmacy preparations and that about 4,000 patients will be eligible for treatment with Skilarence®. If Skilarence® is included on List 1A, this will be accompanied by additional costs of about €7 million in comparison with the existing pharmacy preparations. The following special circumstances apply to this assessment:

- The price of Skilarence® is lower than the ceiling price for the existing cluster and it is four times lower than the price of dimethyl fumarate (Tecfidara®) which has already been included in the cluster.

- Fumarates have been used for decades for the treatment of moderate to severe plaque psoriasis and they are recommended in current Dutch guidelines. Health insurers have reimbursed the pharmacy preparation for some time and the various parties (insurers, the professional group, patients) support the existing practice of using dimethyl fumarate.
- The current NVDV guideline on psoriasis advises consideringfumarates as first choice for the systemic treatment of moderate to severe chronic plaque psoriasis. The guidelines do not distinguish between dimethyl fumarate and MEF/DMF.
- In a phase 3 study (BRIDGE study), the manufacturer demonstrated that the effectiveness and the side effects of Skilarence® [dimethyl fumarate (DMF) monotherapy) and Fumaderm® (MEF/DMF) combination product] are comparable. Based on the same phase 3 study, the EMA concluded that the '*short-term efficacy of Skilarence is considered to have been convincingly demonstrated in comparison to placebo. All three primary objectives of the pivotal study in moderate to severe chronic plaque psoriasis at week 16 were met*'.
- Last but not least: The Medicines Evaluation Board (MEB) wants to minimise off-label use and from this perspective, the initiative to have medicines registered for the indication concerned is appreciated.

Pharmacoeconomic analysis

The above considerations show that the place of treatment of with Skilarence® has been fully worked out and that including Skilarence® on List 1A will only replace the pharmacy preparations. For these reasons the only pharmacoeconomic difference between Skilarence® and the current pharmacy preparations will be a difference in price, so a full pharmacoeconomic analysis would be non-informative in this exceptional case. The difference in price is evident from the budget impact analysis and supplies sufficient information for this application for placing on List 1A. For this reason the *Zorginstituut* did not assess a pharmacoeconomic analysis.

List 2 conditions

If the Ministry of VWS decides to include Skilarence® in a new cluster together with Tecfidera®, then the *Zorginstituut* advises cancelling the Health Insurance Regulation's List 2 conditions for both Tecfidera® and Aubagio® for the indication relapsing remitting multiple sclerosis (RRMS). After all, in practice there is next to no sign that these medicines are being used improperly for multiple sclerosis.

Advice

Based on the current criteria for interchangeability, dimethyl fumarate (Skilarence®) is interchangeable with another medicinal product in the GVS that has the same active substance, namely Tecfidera®.
Thus, in principle, Skilarence® is eligible for inclusion on List 1A in a new cluster with Tecfidera®. This is in keeping with the Ministry's policy to minimise off-label use and to give preference to registered products. However, its inclusion in the GVS will be accompanied by additional costs amounting to approximately €7 million in comparison with the existing pharmacy preparations.
The standard dose of Skilarence® can be fixed at 480 mg.
If Skilarence® is included on List 1A, teriflunomide (Aubagio®) will no longer be interchangeable with dimethyl fumarate, due to a difference in therapeutic area.

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The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.