**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Skilarence 30 mg gastro-resistant tablets
Skilarence 120 mg gastro-resistant tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Skilarence 30 mg
Each gastro-resistant tablet contains 30 mg dimethyl fumarate.
Skilarence 120 mg
Each gastro-resistant tablet contains 120 mg dimethyl fumarate.

Excipient with known effect
Skilarence 30 mg
Each gastro-resistant tablet contains 34.2 mg lactose (as monohydrate).
Skilarence 120 mg
Each gastro-resistant tablet contains 136.8 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Gastro-resistant tablet.
Skilarence 30 mg
White, film-coated, round, biconvex tablet with a diameter of approximately 6.8 mm.
Skilarence 120 mg
Blue, film-coated, round, biconvex tablet with a diameter of approximately 11.6 mm.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Skilarence is indicated for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.

### 4.2 Posology and method of administration

Skilarence is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.

Posology
To improve tolerability, it is recommended to begin treatment with a low initial dose with subsequent gradual increases. In the first week, Skilarence 30 mg is taken once daily (1 tablet in the evening). In the second week, Skilarence 30 mg is taken twice daily (1 tablet in the morning and 1 in the evening). In the third week, Skilarence 30 mg is taken three times daily (1 tablet in the morning, 1 at midday, and 1 in the evening). From the fourth week, treatment is switched to only 1 tablet of Skilarence 120 mg in the evening. This dose is then increased by 1 Skilarence 120 mg tablet per week at different times of day for the subsequent 5 weeks, as shown in the table below. The maximum daily dose allowed is 720 mg (3 x 2 tablets of Skilarence 120 mg).

| Week | Number of tablets | | | Total daily dose (mg) of dimethyl fumarate |
|---|---|---|---|---|
| | Morning | Midday | Evening | |
| **Skilarence 30 mg** | | | | |
| 1 | 0 | 0 | 1 | 30 |
| 2 | 1 | 0 | 1 | 60 |
| 3 | 1 | 1 | 1 | 90 |
| **Skilarence 120 mg** | | | | |
| 4 | 0 | 0 | 1 | 120 |
| 5 | 1 | 0 | 1 | 240 |
| 6 | 1 | 1 | 1 | 360 |
| 7 | 1 | 1 | 2 | 480 |
| 8 | 2 | 1 | 2 | 600 |
| 9+ | 2 | 2 | 2 | 720 |

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 of Skilarence to the maintenance dose required by the individual.

Dosage modifications may also be necessary if abnormalities in laboratory parameters are observed (see section 4.4).

*Elderly patients*
Clinical studies of Skilarence did not include sufficient numbers of patients aged 65 years and above to determine whether they respond differently compared to patients under 65 years (see section 5.2). Based on the pharmacology of dimethyl fumarate, a need for dose adjustment in the elderly is not expected.

*Renal impairment*
No dose adjustment is needed in patients with mild to moderate renal impairment (see section 5.2). Skilarence has not been studied in patients with severe renal impairment, and use of Skilarence is contraindicated in these patients (see section 4.3).

*Hepatic impairment*
No dose adjustment is needed in patients with mild to moderate hepatic impairment (see section 5.2). Skilarence has not been studied in patients with severe hepatic impairment, and use of Skilarence is contraindicated in these patients (see section 4.3).

*Paediatric population*
The safety and efficacy of Skilarence in paediatric patients below the age of 18 years have not been established. There are no data available with Skilarence in paediatric patients.

Method of administration
Skilarence is for oral use.
Skilarence tablets must be swallowed whole with fluid during or immediately after a meal.
The coating of the gastro-resistant tablets is designed to prevent gastric irritation. Therefore, the tablets should not be crushed, divided, dissolved or chewed.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe gastrointestinal disorders.
- Severe hepatic or renal impairment.
- Pregnancy and breast-feeding.

## 4.4 Special warnings and precautions for use

Haematology
Skilarence may decrease leukocyte and lymphocyte counts (see section 4.8). It has not been studied in patients with pre-existing low leukocyte or lymphocyte counts.

*Before treatment*
Prior to initiating treatment with Skilarence, a current complete blood count (including differential blood count and platelet count) should be available. Treatment should not be initiated if leukopenia below $3.0x10^9$/L, lymphopenia below $1.0x10^9$/L or other pathological results are identified.

*During treatment*
During treatment a complete blood count with differential should be performed every 3 months. Action is needed in the following circumstances:

*Leukopenia:* If a marked decrease in the total number of white blood cells is found, the situation should be monitored carefully and treatment with Skilarence should be discontinued at levels below $3.0x10^9$/L.

*Lymphopenia:* If the lymphocyte count falls below $1.0x10^9$/L but is $\geq 0.7\ x10^9$/L, blood monitoring should be performed monthly until levels return to $1.0x10^9$/L or higher for two consecutive blood tests at which point monitoring can again be performed every 3 months.
If the lymphocyte count falls below $0.7x10^9$/L, the blood test must be repeated and if the levels are confirmed to be below $0.7x10^9$/L, then treatment must be stopped immediately. Patients developing lymphopenia should be monitored after stopping treatment until their lymphocyte count has returned to the normal range (see section 4.8).

*Other haematological disorders*
Therapy should be discontinued and caution is advised if other pathological results occur. In any case blood counts should be monitored until values have returned to the normal range.

Infections
Skilarence is an immunomodulator and may affect the way the immune system responds to infection. For patients with pre-existing infections of clinical relevance, the physician should decide if treatment with Skilarence should only be initiated once the infection has resolved. If a patient develops an infection during treatment with Skilarence, suspension of treatment should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Patients receiving Skilarence should be instructed to report symptoms of infection to a physician.

*Opportunistic infections/progressive multifocal leukoencephalopathy (PML)*
Cases of opportunistic infections, particularly of progressive multifocal leukoencephalopathy (PML) have been reported with other dimethyl fumarate-containing products (see section 4.8). PML is an opportunistic infection caused by the John-Cunningham virus (JCV) that can be fatal or cause severe disabilities. PML is probably caused by a combination of factors.

A previous infection with JCV is considered a prerequisite for the development of PML. Risk factors can include previous immunosuppressive treatment and the existence of certain concomitant disorders (such as some autoimmune disorders or malignant haematological conditions). A modified or weakened immune system as well as genetic or environmental factors can also constitute risk factors.

Persistent moderate or severe lymphopenia during treatment with dimethyl fumarate is also considered a risk factor for PML. Patients who develop lymphopenia should be monitored for signs and symptoms of opportunistic infections, particularly for symptoms indicative of PML. Typical symptoms associated with PML are diverse, become worse over days to weeks and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision and changes in thinking, memory and orientation leading to confusion and personality changes. If PML is suspected, treatment with Skilarence should be stopped immediately and further appropriate neurological and radiological examinations performed.

Prior and concomitant treatment with immunosuppressive or immunomodulating therapies
Limited data are available on the efficacy and safety of Skilarence in patients who have been previously treated with other immunosuppressive or immunomodulating therapies. When switching patients from such therapies to Skilarence, the half-life and mode of action of the other therapy should be considered in order to avoid additive effects on the immune system.

No data are available on the efficacy and safety of Skilarence when taken concomitantly with other immunosuppressive or immunomodulating therapies (see section 4.5).

Pre-existing gastrointestinal disease
Skilarence has not been studied in patients with pre-existing gastrointestinal disease. Skilarence is contraindicated in patients with severe gastrointestinal disease (see sections 4.3). Gastrointestinal tolerability can be improved by following the dose titration schedule on initiating Skilarence treatment and by taking Skilarence with food (see sections 4.2 and 4.8).

Renal function
Since renal elimination plays a minor role in the clearance of Skilarence from plasma, it is unlikely that renal impairment would affect the pharmacokinetic characteristics, and so a need for dose adjustment in patients with mild to moderate renal impairment is not expected (see sections 4.2 and 5.2).

During the Phase III placebo-controlled clinical trial, renal function was not seen to deteriorate during therapy across treatment groups. However, Skilarence has not been studied in patients with severe renal impairment, and some cases of renal toxicity have been reported during post-marketing surveillance with fumaric acid esters. Hence, Skilarence is contraindicated in patients with severe renal impairment (see section 4.3).

Renal function (e.g. creatinine, blood urea nitrogen and urinalysis) should be checked prior to initiation of treatment and every 3 months thereafter. In the event of a clinically relevant change in renal function, particularly in the absence of alternative explanations, consideration should be given to dosage reduction or treatment discontinuation.

*Fanconi syndrome*
Early diagnosis of Fanconi syndrome and discontinuation of Skilarence treatment are important to prevent the onset of renal impairment and osteomalacia, as the syndrome is usually reversible. The most important signs are: proteinuria, glucosuria (with normal blood sugar levels), hyperaminoaciduria and phosphaturia (possibly concurrent with hypophosphatemia). Progression might involve symptoms such as polyuria, polydipsia and proximal muscle weakness. In rare cases hypophosphataemic osteomalacia with non-localised bone pain, elevated alkaline phosphatase in serum and stress fractures may occur. Importantly, Fanconi syndrome can occur without elevated creatinine levels or low glomerular filtration rate. In case of unclear symptoms Fanconi syndrome should be considered and appropriate examinations should be performed.

Hepatic function
Skilarence has not been studied in patients with severe hepatic impairment and is contraindicated in these patients (see section 4.3).

It is recommended to monitor hepatic function (SGOT, SGPT, gamma-GT, AP) prior to initiation of

treatment and every 3 months thereafter, since elevation of hepatic enzymes has been observed in some patients in the Phase III study. In the event of a clinically relevant change in hepatic parameters, particularly in the absence of alternative explanations, consideration should be given to dose reduction or treatment discontinuation.

Flushing
Patients should be made aware that they are likely to experience flushing in the first few weeks of taking Skilarence (see section 4.8).

Lactose
Skilarence contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Skilarence should be used cautiously in combination with other systemic antipsoriatic therapy (e.g. methotrexate, retinoids, psoralens, ciclosporin, immunosuppressants or cytostatics) (see section 4.4). During treatment with Skilarence, simultaneous use of other fumaric acid derivatives (topical or systemic) should be avoided.

Concurrent therapy with nephrotoxic substances (e.g. methotrexate, ciclosporin, aminoglycosides, diuretics, NSAIDs or lithium) may increase the potential for renal adverse reactions (e.g. proteinuria) in patients taking Skilarence.

In cases of severe or prolonged diarrhoea during treatment with Skilarence, absorption of other medicinal products may be affected. Caution should be exercised when prescribing medicinal products with a narrow therapeutic index that require absorption in the intestinal tract. The efficacy of oral contraceptives may be reduced and the use of an alternative barrier contraceptive method is recommended to prevent possible failure of contraception (see the prescribing information of the oral contraceptive).

Consumption of large quantities of strong alcoholic drinks (more than 30% alcohol by volume) should be avoided because it may lead to increased dissolution rates of Skilarence and, therefore, may increase the frequency of gastrointestinal adverse reactions.

Vaccination during treatment with Skilarence has not been studied. Immunosuppression is a risk factor for the use of live vaccines. The risk of vaccination should be weighed against the benefit.

There is no evidence for Skilarence interaction with cytochrome P450 and the most common efflux and uptake transporters, thus no interactions are expected with medicinal products metabolised or transported by these systems (see section 5.2).

## 4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
Skilarence is not recommended in women of child-bearing potential not using appropriate contraception. In patients experiencing diarrhoea during Skilarence treatment, the effect of oral contraceptives may be reduced and additional barrier methods of contraception may be necessary (see section 4.5).

Pregnancy
There are limited data from the use of dimethyl fumarate in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Skilarence is contraindicated during pregnancy (see section 4.3).

Breast-feeding
It is unknown whether dimethyl fumarate or its metabolites are excreted in human milk. A risk to newborns or infants cannot be excluded. Therefore, Skilarence is contraindicated during breast-feeding (see section 4.3).

Fertility
There are no human or animal data on the effects of Skilarence on fertility.

## 4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been conducted. Skilarence may have a minor influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of Skilarence (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions observed with Skilarence in the Phase III clinical study (1102) in psoriasis patients were gastrointestinal events (62.7%), flushing (20.8%) and lymphopenia (10.0%). Most adverse reactions were considered mild and did not lead to discontinuation of study treatment. The only adverse reactions that led to discontinuation of treatment in >5% of patients were gastrointestinal reactions. For monitoring recommendations and clinical management of adverse reactions, see section 4.4.

Tabulated list of adverse reactions
The following is a list of adverse reactions experienced by patients treated with Skilarence during the clinical study and with Fumaderm, a related medicinal product containing dimethyl fumarate along with other fumaric acid esters.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data).

| System organ class | Adverse reactions | Frequency |
|---|---|---|
| Blood and lymphatic system disorders | Lymphopenia | Very common |
| | Leukopenia | Very common |
| | Eosinophilia | Common |
| | Leukocytosis | Common |
| | Acute lymphatic leukaemia* | Very rare |
| | Irreversible pancytopenia* | Very rare |
| Metabolism and nutrition disorders | Decreased appetite | Common |
| Nervous system disorders | Headache | Common |
| | Paraesthesia | Common |
| | Dizziness* | Uncommon |
| | Progressive multifocal leukoencephalopathy* | Not known |
| Vascular disorders | Flushing | Very common |
| Gastrointestinal disorders | Diarrhoea | Very common |
| | Abdominal distension* | Very common |
| | Abdominal pain | Very common |
| | Nausea | Very common |
| | Vomiting | Common |
| | Dyspepsia | Common |
| | Constipation | Common |
| | Abdominal discomfort | Common |

| System organ class | Adverse reactions | Frequency |
|---|---|---|
| | Flatulence | Common |
| Skin and subcutaneous tissue disorders | Erythema<br>Skin burning sensation<br>Pruritus<br>Allergic skin reaction* | Common<br>Common<br>Common<br>Rare |
| Renal and urinary disorders | Proteinuria*<br>Renal failure*<br>Fanconi syndrome* | Uncommon<br>Not known<br>Not known |
| General disorders and administration site conditions | Fatigue<br>Feeling hot<br>Asthenia | Common<br>Common<br>Common |
| Investigations | Hepatic enzymes increased<br>Serum creatinine increased* | Common<br>Uncommon |

*Additional adverse reactions reported with Fumaderm, a related medicinal product containing dimethyl fumarate along with other fumaric acid esters.

Description of selected adverse reactions

*Gastrointestinal disturbances*

Data from the Phase III clinical study as well as from the literature show that gastrointestinal disorders with dimethyl fumarate-containing products are most likely to occur during the first 2 to 3 months after starting treatment. No apparent dose relationship and no risk factors for the occurrence of these adverse reactions could be identified. Diarrhoea was a common adverse reaction (36.9%) among patients taking Skilarence, leading to medicinal product withdrawal in about 10% of patients. More than 90% of these diarrhoea events were of mild to moderate severity (see section 4.4).

*Flushing*

Based on observations in the Phase III clinical study as well as on literature data, flushing is most likely to occur during the early weeks of treatment and tends to lessen with time. In the clinical study a total of 20.8% of patients receiving Skilarence experienced flushing, which was mild in the majority of cases (see section 4.4). Published clinical experience with dimethyl fumarate-containing products shows that individual episodes of flushing usually begin shortly after taking the tablets and resolve within a few hours.

*Haematological changes*

Data from the Phase III clinical study as well as from the literature show that changes in haematological parameters are most likely to occur during the first 3 months after starting treatment with dimethyl fumarate. In particular, in the clinical study there was a slight decrease in mean lymphocyte counts starting between weeks 3 and 5 and reaching a maximum in week 12 where approximately one third of patients had lymphocyte values below $1.0x10^9$/L. The mean and median values of lymphocytes remained within the normal range during the clinical study. At week 16 (end of treatment), there was no further decline in lymphocyte counts. At week 16 of treatment, 13/175 (7.4%) of patients were noted to have lymphocyte levels $<0.7x\ 10^9$/L. Blood sampling for safety clinical laboratory tests at follow-up visits was only performed in case of abnormalities at the preceeding visit. During the treatment free follow up, lymphocyte levels of $<0.7x\ 10^9$/L were observed in 1/29 (3.5%) patient at 6 months and 0/28 (0%) at 12 months after stopping treatment. At 12 months after stopping treatment 3/28 (10.7%) of patients had lymphocyte values below $1.0x10^9$/L, which would represent 3/279 (1.1%) of the patients started on Skilarence.

For the total leukocyte count, a decline became apparent at week 12 of treatment; it slowly increased again at week 16 (end of treatment); and 12 months after stopping treatment all patients had values above $3.0x10^9$/L.

A transient increase in mean values of eosinophils was noted as early as week 3, reached a maximum at week 5 and 8, and had returned to baseline values at week 16.

For monitoring recommendations and clinical management of haematological adverse reactions, see section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Symptomatic treatment is indicated in the case of an overdose. No specific antidote is known.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: not yet assigned

Mechanism of action
The anti-inflammatory and immunomodulating effects of dimethyl fumarate and its metabolite monomethyl fumarate are not fully elucidated but are thought to be mainly due to the interaction with the intracellular reduced glutathione of cells directly involved in the pathogenesis of psoriasis. This interaction with glutathione leads to the inhibition of translocation into the nucleus and the transcriptional activity of the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB).

The main activity of dimethyl fumarate and monomethyl fumarate is considered to be immunomodulatory, resulting in a shift in T helper cells (Th) from the Th1 and Th17 profile to a Th2 phenotype. The inflammatory cytokine production is reduced with induction of proapoptotic events, inhibition of keratinocyte proliferation, reduced expression of adhesion molecules, and diminished inflammatory infiltrate within psoriatic plaques.

Clinical efficacy and safety
The safety and efficacy of Skilarence was assessed in one double-blind, 3-arm, placebo- and active comparator-controlled Phase III study (1102) in patients with moderate to severe plaque psoriasis (Study 1102). 704 patients were randomised to receive Skilarence, an active comparator (Fumaderm, a combination product with the same content of dimethyl fumarate plus 3 monoethyl fumarate salts) and placebo in a ratio of 2:2:1. Patients began treatment with tablets containing 30 mg/day dimethyl fumarate or placebo, titrating up to a maximum of 720 mg/day in both active treatment arms as described in section 4.2. If treatment success was observed before the maximum dose of 720 mg/day of dimethyl fumarate was reached, no further increase of dosage was necessary and the dosage was to be steadily reduced to an individual maintenance dose. In case of individual intolerability of the increased dosage during weeks 4 to 16, the patient was to return to the last tolerated dose taken since the start of week 4, which was to be maintained until end of the treatment period (week 16). Patients received treatment for up to 16 weeks and follow-up visits were planned for up to 12 months after treatment was stopped.

The demographic and baseline characteristics were well balanced between the treatment groups. Of the 699 patients, most were Caucasian (99%) and male (65%), and the mean age was 44 years. Most patients (91%) were <65 years of age. Most patients had moderate psoriasis based on Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA) scores at baseline: the mean PASI score at baseline was 16.35 and 60% of patients scored as moderate on the PGA. The majority of patients reported a "very large" or "extremely large" effect of psoriasis on their life based on the Dermatology Life Quality Index (DLQI), with a mean DLQI score of 11.5.

After 16 weeks of treatment, Skilarence was found to be superior to placebo ($p<0.0001$) based on

PASI 75 and PGA score clear or almost clear and non-inferior (using a non-inferiority margin of -15%) to the active comparator ($p<0.0003$) based on PASI 75.

**Summary of clinical efficacy after 16 weeks treatment in Study 1102**

| **Assessment** | **Skilarence N=267** | **Placebo N=131** | **Fumaderm N=273** |
|---|---|---|---|
| **Superiority testing vs placebo** | | | |
| **PASI 75**, n (%) | 100 (37.5) | 20 (15.3) | 110 (40.3) |
| p-value | | <0.0001[a] | <0.0001[a] |
| Two-sided 99.24% CI | | 10.7, 33.7[a] | 13.5, 36.6[a] |
| **PGA score clear or almost clear,** n (%) | 88 (33.0) | 17 (13.0) | 102 (37.4) |
| p-value | | <0.0001[a] | <0.0001[a] |
| Two-sided 99.24% CI | | 9.0, 31.0 [a] | 13.3, 35.5 [a] |

| | **Skilarence N=267** | **Fumaderm N=273** |
|---|---|---|
| **Non-inferiority of Skilarence vs. Fumaderm** | | |
| **PASI 75**, n (%) | 100 (37.5) | 110 (40.3) |
| p-value | 0.0003[b] | |
| One-sided 97.5% repeated CI (lower limit) | -11.6[b] | |
| **PGA score clear or almost clear,** n (%) | 88 (33.0) | 102 (37.4) |
| p-value | 0.0007[b] | |
| One-sided 97.5% repeated CI (lower limit) | -13.0[b] | |

Fumaderm = Active comparator, a combination product with the same content of dimethyl fumarate plus 3 monoethyl hydrogen fumarate salts; n=number of patients with available data; N=number of patients in population; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; [a] Superiority of Skilarence vs. Placebo with a difference of 22.2% for PASI 75 and 20.0% for PGA score clear or almost clear, superiority of Fumaderm vs Placebo with a difference of 25.0% for PASI 75 and 24.4% for PGA score clear or almost clear; [b] Non-inferiority of Skilarence vs. Fumaderm with a difference of -2.8% for PASI 75 and -4.4% for PGA score clear or almost clear.

There was a trend in the efficacy endpoint PASI score mean % change from baseline, indicating the onset of a clinical response to Skilarence as early as week 3 (-11.8%) which became statistically significant compared to placebo by week 8 (-30.9%). Further improvement was seen by week 16 (-50.8%).

The benefits of treatment with Skilarence were also supported by patient self-perceived improvements in their quality of life. At week 16, patients treated with Skilarence had a lower mean DLQI compared to placebo (5.4 vs 8.8).

Rebound (defined as worsening of ≥125% of baseline PASI value) was assessed after 2 months off treatment and was shown not to be a clinical concern with fumaric acid esters, as it was documented in very few patients (Skilarence 1.1% and active comparator 2.2%, compared to 9.3% in the placebo group).

Long-term efficacy data are currently not available for Skilarence, however, in the pharmacokinetic and clinical studies the systemic exposure, efficacy and safety of Skilarence were shown to be comparable to the active comparator containing dimethyl fumarate. Hence it is reasonable to expect the long-term efficacy of Skilarence to also be comparable to dimethyl fumarate-containing products. Maintenance of long term efficacy has been well described for other dimethyl fumarate-containing products, and therefore the treatment benefits seen with Skilarence at 16 weeks can be expected to be maintained in patients treated over the long term for at least 24 months.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Skilarence in all subsets of the paediatric population in this indication (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption
After oral administration, dimethyl fumarate is not detected in plasma because it is rapidly hydrolysed by esterases to its active metabolite monomethyl fumarate. After oral administration of a single Skilarence 120 mg tablet in healthy subjects, monomethyl fumarate reached plasma peak concentrations of around 1325 ng/mL and 1311 ng/mL under fasted or fed conditions, respectively. Taking Skilarence with food delayed the $t_{max}$ of monomethyl fumarate from 3.5 to 9.0 hours.

Distribution
The plasma protein binding of monomethyl fumarate is around 50%. Dimethyl fumarate does not show any binding affinity to serum proteins which may further contribute to its rapid elimination from the circulation.

Biotransformation
The biotransformation of dimethyl fumarate does not involve cytochrome P450 isoenzymes. *In vitro* studies have shown that monomethyl fumarate at the therapeutic dose does not inhibit or induce any of the cytochrome P450 enzymes, it is not a substrate or inhibitor of P-glycoprotein and is not an inhibitor of the most common efflux and uptake transporters. In vitro studies have shown that dimethyl fumarate at a therapeutic dose does not inhibit CYP3A4/5 and BCRP and is a weak P-glycoprotein inhibitor.

*In vitro* studies have shown that hydrolysis of dimethyl fumarate to monomethyl fumarate occurs rapidly at pH 8 (pH in the small intestine), but not at pH 1 (pH in the stomach). A part of the total dimethyl fumarate is hydrolysed by esterases and the alkaline milieu of the small intestine, while the remainder enters the portal vein blood. Further studies have shown that dimethyl fumarate (and to a lesser extent monomethyl fumarate) reacts partially with reduced glutathione forming a glutathione-adduct. These adducts were detected in animal studies in the intestinal mucosa of rats and to a smaller extent in portal vein blood. Unconjugated dimethyl fumarate, however, cannot be detected in the plasma of animals or psoriatic patients following oral administration. By contrast, unconjugated monomethyl fumarate is detectable in plasma. Further metabolism occurs through oxidation via the tricarboxylic acid cycle forming carbon dioxide and water.

Elimination
Exhalation of $CO_2$ resulting from the metabolism of monomethyl fumarate is the primary route of elimination; only small amounts of intact monomethyl fumarate are excreted through urine or faeces. The portion of dimethyl fumarate that reacts with glutathione, forming a glutathione-adduct, is metabolised further to its mercapturic acid, which is excreted in the urine.

The apparent terminal elimination half-life of monomethyl fumarate is about 2 hours.

Linearity/non-linearity
Despite the high inter-subject variability, the exposure measured as AUC and $C_{max}$ was generally dose-proportional after single dose administration of 4 x 30 mg dimethyl fumarate tablets (total dose of 120 mg) and 2 x 120 mg dimethyl fumarate tablets (total dose of 240 mg).

Renal impairment
No specific studies have been performed in patients with renal impairment. However, because renal elimination plays a minor role in the total clearance from plasma, it is unlikely that renal impairment may affect the pharmacokinetic characteristics of Skilarence (see section 4.2).

Hepatic impairment
No specific studies have been performed in patients with hepatic impairment. However, as dimethyl fumarate is metabolised by esterases and the alkaline milieu of the small intestine without the involvement of cytochrome P450, hepatic impairment is not expected to influence exposure (see section 4.2).

## 5.3 Preclinical safety data

Non-clinical safety pharmacology and genotoxicity data reveal no special hazard for humans.

Toxicology
The kidney was identified as a major target organ of toxicity in non-clinical studies. Renal findings in dogs included minimal to moderate tubular hypertrophy, increased incidence and severity of tubular vacuolation and minimal to slight tubular degeneration, which were considered toxicologically relevant. The no-observed adverse-effect-level (NOAEL) after 3 months of treatment was 30 mg/kg/day, which corresponds to 2.9-fold and 9.5-fold the human systemic exposure at the highest recommended dose (720 mg/day), as AUC and $C_{max}$ values, respectively.

Reproduction toxicity
No fertility or pre- and post-natal development studies have been conducted with Skilarence.

There were no effects on foetal body weights or malformations attributed to maternal administration of dimethyl fumarate during the embryo-foetal development study in rats. However, there was an increased number of foetuses with the variations “supernumerary liver lobe” and “abnormal iliac alignment” at maternally toxic doses. The NOAEL for maternal and embryo-foetal toxicity was 40 mg/kg/day, corresponding to 0.2-fold and 2.0-fold the human systemic exposure at the highest recommended dose (720 mg/day), as AUC and $C_{max}$ values, respectively.

Dimethyl fumarate has been shown to cross the placental membrane into foetal blood in rats.

Carcinogenicity
No carcinogenicity studies have been performed for Skilarence. Based on available data suggesting that fumaric acid esters may activate cellular pathways related to the development of renal tumours, a potential tumorigenic activity of exogenously administered dimethyl fumarate on the kidneys cannot be excluded.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Skilarence 30 mg and Skilarence 120 mg
*Core:*
Lactose monohydrate
Cellulose microcrystalline
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Skilarence 30 mg
*Coating:*
Methacrylic acid-ethyl acrylate copolymer (1:1)
Talc
Triethyl citrate
Titanium dioxide (E171)
Simethicone

Skilarence 120 mg
*Coating:*
Methacrylic acid-ethyl acrylate copolymer (1:1)
Talc
Triethyl citrate
Titanium dioxide (E171)
Simethicone
Indigo carmine (E132)
Sodium hydroxide

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Skilarence 30 mg
42, 70 and 210 gastro-resistant tablets in PVC/PVDC-aluminium blister packs.

Skilarence 120 mg
40, 70, 90, 100, 120, 180, 200, 240, 300, 360 and 400 gastro-resistant tablets in PVC/PVDC-aluminium blister packs.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7. MARKETING AUTHORISATION HOLDER

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona
Spain

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1201/001
EU/1/17/1201/002
EU/1/17/1201/003
EU/1/17/1201/004
EU/1/17/1201/005
EU/1/17/1201/006
EU/1/17/1201/007
EU/1/17/1201/008
EU/1/17/1201/009

EU/1/17/1201/010
EU/1/17/1201/011
EU/1/17/1201/012
EU/1/17/1201/013
EU/1/17/1201/014

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 june 2017

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Industrias Farmaceuticas Almirall, S.A.
Ctra. Nacional II, Km. 593, Sant Andreu de la Barca, Barcelona,
08740, Spain

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Skilarence in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objectives of the educational programme are to inform health care professionals about the risk of serious infections, mainly opportunistic infections such as progressive multifocal leukoencephalopathy (PML), and to provide guidance on the monitoring of lymphocyte and leukocyte count abnormalities.

The MAH shall ensure that in each Member State where Skilarence is marketed, healthcare professionals who are expected to prescribe and dispense Skilarence have access to the following

educational package.

- **The guide for healthcare professionals** shall contain the following key elements:
  - Relevant information on PML (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable)
  - Details of the population at higher risk for PML
  - Details on how to minimise the risk of PML through appropriate monitoring and management, including laboratory monitoring of lymphocyte and leukocyte prior to and during treatment, and criteria for treatment discontinuation
  - Key messages to convey in counselling of patients

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

## A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON - SKILARENCE 30 mg GASTRO RESISTANT TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Skilarence 30 mg gastro-resistant tablets
dimethyl fumarate

## 2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 30 mg dimethyl fumarate.

## 3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

42 gastro-resistant tablets
70 gastro-resistant tablets
210 gastro-resistant tablets

## 5. METHOD AND ROUTE OF ADMINISTRATION

Do not crush, break, dissolve or chew the tablet.

Read the package leaflet before use.

Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona
Spain

## 12. MARKETING AUTHORISATION NUMBER

EU/1/17/1201/001 42 tablets
EU/1/17/1201/013 70 tablets
EU/1/17/1201/014 210 tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skilarence 30 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL - SKILARENCE 30 mg GASTRO RESISTANT TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Skilarence 30 mg gastro-resistant tablets
dimethyl fumarate

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Almirall

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON - SKILARENCE 120 mg GASTRO RESISTANT TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Skilarence 120 mg gastro-resistant tablets
dimethyl fumarate

## 2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 120 mg dimethyl fumarate.

## 3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

40 gastro-resistant tablets
70 gastro-resistant tablets
90 gastro-resistant tablets
100 gastro-resistant tablets
120 gastro-resistant tablets
180 gastro-resistant tablets
200 gastro-resistant tablets
240 gastro-resistant tablets
300 gastro-resistant tablets
360 gastro-resistant tablets
400 gastro-resistant tablets

## 5. METHOD AND ROUTE OF ADMINISTRATION

Do not crush, break, dissolve or chew the tablet.

Read the package leaflet before use.

Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona
Spain

## 12. MARKETING AUTHORISATION NUMBERS

| | |
|---|---|
| EU/1/17/1201/002 | 40 tablets |
| EU/1/17/1201/003 | 70 tablets |
| EU/1/17/1201/004 | 90 tablets |
| EU/1/17/1201/005 | 100 tablets |
| EU/1/17/1201/006 | 120 tablets |
| EU/1/17/1201/007 | 180 tablets |
| EU/1/17/1201/008 | 200 tablets |
| EU/1/17/1201/009 | 240 tablets |
| EU/1/17/1201/012 | 300 tablets |
| EU/1/17/1201/010 | 360 tablets |
| EU/1/17/1201/011 | 400 tablets |

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skilarence 120 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL - SKILARENCE 120 mg GASTRO RESISTANT TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Skilarence 120 mg gastro-resistant tablets
dimethyl fumarate

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Almirall

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Skilarence 30 mg gastro-resistant tablets**
dimethyl fumarate

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Skilarence is and what it is used for

**What Skilarence is**
Skilarence is a medicine that contains the active substance dimethyl fumarate. Dimethyl fumarate works on cells of the immune system (the body's natural defences). It changes the activity of the immune system and reduces the production of substances involved in causing psoriasis.

**What Skilarence is used for**
Skilarence tablets are used to treat moderate to severe plaque psoriasis in adults. Psoriasis is a disease causing thickened, inflamed, red areas on the skin, often covered by silvery scales.

Response to Skilarence can be generally seen as early as week 3 and improves over time. Experience with related products containing dimethyl fumarate shows treatment benefit for at least up to 24 months.

## 2. What you need to know before you take Skilarence

**Do not take Skilarence**
- if you are allergic to dimethyl fumarate or any of the other ingredients of this medicine (listed in section 6)
- if you have severe problems with your stomach or intestines
- if you have severe liver or kidney problems
- if you are pregnant or breast-feeding

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Skilarence.

Monitoring
Skilarence may cause problems with your blood, liver or kidneys. You will have blood and urine tests before treatment and then regularly during your treatment to make sure that you are not getting these

complications and can continue to take this medicine. Depending on the results of these blood and urine tests, your doctor may reduce your dose of Skilarence or stop treatment.

Infections
White blood cells help your body to fight infections. Skilarence may reduce the number of your white blood cells. Talk to your doctor if you think you may have an infection. Symptoms include fever, pain, aching muscles, headache, loss of appetite and a general feeling of weakness. If you have a serious infection, either before starting treatment with Skilarence or during treatment, your doctor may advise you not to take Skilarence until the infection has resolved.

Gastrointestinal disorders
Tell your doctor if you have or have had problems with your stomach or intestines. Your doctor will advise you on what care you need to take during Skilarence treatment.

**Children and adolescents**
Children and adolescents below the age of 18 years should not take this medicine because it has not been studied in this age group.

**Other medicines and Skilarence**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking the following:

- **Dimethyl fumarate or other fumarates.** The active ingredient in Skilarence, dimethyl fumarate, is also used in other medicines such as tablets, ointments and baths. You must avoid using other products that contain fumarates to prevent taking too much.
- **Other medicines used to treat psoriasis,** such as methotrexate, retinoids, psoralens, ciclosporin, or other immunosuppressants or cytostatics (medicines that affect the immune system). Taking these medicines with Skilarence could increase the risk of side effects on your immune system.
- **Other medicines that can affect your kidney function,** such as methotrexate or ciclosporin (used to treat psoriasis), aminoglycosides (used to treat infections), diuretics (which increase urine), nonsteroidal anti-inflammatory drugs (used to treat pain) or lithium (used for bipolar disease and depression). These medicines taken together with Skilarence could increase the risk of side effects on your kidneys.

If you get severe or prolonged diarrhoea with Skilarence, other medicines may not work as well as they should. Talk to your doctor if you have bad diarrhoea and are concerned that other medicines you are taking might not work. In particular, if you are taking a contraceptive medicine (the pill), the effect may be reduced and you may need to use other barrier methods to prevent pregnancy. See the instructions in the patient leaflet of the contraceptive you are taking.

If you need a vaccination, talk to your doctor. Certain types of vaccines (live vaccines) may cause infection if used during treatment with Skilarence. Your doctor can advise you what would be best.

**Skilarence with alcohol**
Avoid strong alcoholic drinks (more than 50 ml of spirits containing more than 30% alcohol by volume) during treatment with Skilarence, as alcohol can interact with this medicine. This could cause stomach and intestinal problems.

**Pregnancy and breast-feeding**
Do not take Skilarence if you are pregnant or trying to become pregnant, as Skilarence may harm your baby. Use effective methods of contraception to avoid becoming pregnant during treatment with Skilarence (see also “Other medicines and Skilarence” above).
Do not breast-feed during treatment with Skilarence.

**Driving and using machines**
Skilarence may have a minor influence on the ability to drive and use machines. You may feel dizzy or tired after taking Skilarence. If you are affected, be careful when driving or using machines.

**Skilarence contains lactose**
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

**Skilarence contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

## 3. How to take Skilarence

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**Dose**
Your doctor will start your treatment with a low dose (using 30 mg Skilarence tablets). This helps to reduce stomach problems and other side effects. Your dose will be increased every week as shown in the table below (switching to 120 mg Skilarence tablets from week 4 onwards).

| Treatment week | Tablet strength | How many tablets to take during the day | | | Number of tablets per day | Total daily dose |
|---|---|---|---|---|---|---|
| | | Breakfast | Lunch | Evening meal | | |
| 1 | 30 mg | – | – | 1 | 1 | 30 mg |
| 2 | 30 mg | 1 | – | 1 | 2 | 60 mg |
| 3 | 30 mg | 1 | 1 | 1 | 3 | 90 mg |
| 4 | 120 mg | – | – | 1 | 1 | 120 mg |
| 5 | 120 mg | 1 | – | 1 | 2 | 240 mg |
| 6 | 120 mg | 1 | 1 | 1 | 3 | 360 mg |
| 7 | 120 mg | 1 | 1 | 2 | 4 | 480 mg |
| 8 | 120 mg | 2 | 1 | 2 | 5 | 600 mg |
| 9+ | 120 mg | 2 | 2 | 2 | 6 | 720 mg |

Your doctor will check how well your condition is improving after you start taking Skilarence and will check for side effects. If you have severe side effects after an increase in dose, your doctor may recommend that you temporarily go back to the last dose. If the side effects are not troublesome, your dose will be increased until your condition is well controlled. You may not need the maximum dose of 720 mg per day. After your condition has improved sufficiently, your doctor will consider how to gradually reduce the daily dose of Skilarence to what you need to maintain your improvement.

**Method of administration**
Swallow Skilarence tablets whole with liquid. Take your tablets during or immediately after a meal. Do not crush, break, dissolve or chew your tablets, as they have a special coating to help prevent irritation of your stomach.

**If you take more Skilarence than you should**
If you think you have taken too many Skilarence tablets, talk to your doctor or pharmacist.

**If you forget to take Skilarence**
Do not take a double dose to make up for a forgotten dose. Take the next dose at the usual time and continue taking the medicine exactly as described in this leaflet or exactly as agreed with your doctor. Please ask your doctor or pharmacist if you are not sure.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these side effects, such as reddening of the face or body (flushing), diarrhoea, stomach problems and nausea usually improve as you continue treatment.

The most serious side effects that may occur with Skilarence are allergic or hypersensitivity reactions; kidney failure or a kidney disease called Fanconi syndrome; or a severe brain infection called progressive multifocal leukoencephalopathy (PML). It is not known how commonly they occur. For symptoms see below.

Allergic or hypersensitivity reactions
Allergic or hypersensitivity reactions are rare but may be very serious. Reddening of the face or body (flushing) is a very common side effect which may affect more than 1 in 10 people. However, if you become flushed and get any of the following signs:
- wheezing, difficulty breathing or shortness of breath,
- swelling of the face, lips, mouth or tongue

stop taking Skilarence and call a doctor straight away.

Brain infection called PML
Progressive multifocal leukoencephalopathy (PML) is a rare but serious brain infection that can lead to severe disability or death. If you notice new or worsening weakness on one side of the body; clumsiness; changes in vision, thinking or memory; confusion; or personality changes lasting several days, stop taking Skilarence and talk to your doctor straight away.

Fanconi syndrome
Fanconi syndrome is a rare but serious kidney disorder which may occur with Skilarence. If you notice you are passing more urine, are more thirsty and drinking more than normal, your muscles seem weaker, you break a bone, or just have aches and pains, talk to your doctor as soon as possible so that this can be investigated further.

Talk to your doctor if you get any of the following side effects.

Very common side effects (may affect more than 1 in 10 people):
- decrease in white blood cells called lymphocytes (lymphopenia)
- decrease in all white blood cells (leukopenia)
- reddening of the face or body (flushing)
- diarrhoea
- bloating, stomach pain or stomach cramps
- feeling sick (nausea)

Common side effects (may affect up to 1 in 10 people):
- increase in all white blood cells (leukocytosis)
- increase in specific white blood cells called eosinophils
- increase in certain enzymes in the blood (used for checking the health of your liver)
- being sick

- constipation
- gas (flatulence), stomach discomfort, indigestion
- decreased appetite
- headache
- feeling tired
- weakness
- feeling hot
- abnormal sensations of the skin, such as itching, burning, stinging, tickling or tingling
- pink or red blotches on the skin (erythema)

Uncommon side effects (may affect up to 1 in 100 people):
- dizziness
- excess protein in the urine (proteinuria)
- increase in serum creatinine (a substance in the blood used for measuring how well your kidneys are working)

Rare side effects (may affect up to 1 in 1,000 people):
- allergic skin reaction

Very rare side effects (may affect up to 1 in 10,000 people):
- acute lymphatic leukaemia (a type of blood cancer)
- decrease in all types of blood cells (pancytopenia)

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Skilarence

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Skilarence 30 mg contains**
- the active substance is dimethyl fumarate. One tablet contains 30 mg dimethyl fumarate.
- the other ingredients are: lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, methacrylic acid-ethyl acrylate copolymer (1:1), talc, triethyl citrate, titanium dioxide (E171) and simethicone.

**What Skilarence 30 mg looks like and contents of the pack**
Skilarence 30 mg is a white, round tablet with a diameter of approximately 6.8 mm.
Skilarence 30 mg is available in packs containing 42, 70 and 210 gastro-resistant tablets. Not all pack sizes may be marketed. The tablets are packed in PVC/PVDC-aluminium blisters.

**Marketing Authorisation Holder**
Almirall, S.A.
Ronda General Mitre, 151
E-08022 Barcelona
Spain
Tel. +34 93 291 30 00

**Manufacturer**
Industrias Farmacéuticas Almirall, S.A.
Ctr. Nacional II, Km. 593
E-08740 Sant Andreu de la Barca, Barcelona
Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien/ Luxembourg/Luxemburg**
Almirall N.V., Tél/Tel: +32 (0)2 771 86 37

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**United Kingdom**
Almirall Limited, Tel: +44 (0) 800 0087 399

**This leaflet was last revised in** .

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

**Package leaflet: Information for the patient**

**Skilarence 120 mg gastro-resistant tablets**
dimethyl fumarate

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Skilarence is and what it is used for

**What Skilarence is**
Skilarence is a medicine that contains the active substance dimethyl fumarate. Dimethyl fumarate works on cells of the immune system (the body's natural defences). It changes the activity of the immune system and reduces the production of substances involved in causing psoriasis.

**What Skilarence is used for**
Skilarence tablets are used to treat moderate to severe plaque psoriasis in adults. Psoriasis is a disease causing thickened, inflamed, red areas on the skin, often covered by silvery scales.

Response to Skilarence can be generally seen as early as week 3 and improves over time. Experience with related products containing dimethyl fumarate shows treatment benefit for at least up to 24 months.

## 2. What you need to know before you take Skilarence

**Do not take Skilarence**
- if you are allergic to dimethyl fumarate or any of the other ingredients of this medicine (listed in section 6)
- if you have severe problems with your stomach or intestines
- if you have severe liver or kidney problems
- if you are pregnant or breast-feeding

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Skilarence.

Monitoring
Skilarence may cause problems with your blood, liver or kidneys. You will have blood and urine tests before treatment and then regularly during your treatment to make sure that you are not getting these

complications and can continue to take this medicine. Depending on the results of these blood and urine tests, your doctor may reduce your dose of Skilarence or stop treatment.

Infections
White blood cells help your body to fight infections. Skilarence may reduce the number of your white blood cells. Talk to your doctor if you think you may have an infection. Symptoms include fever, pain, aching muscles, headache, loss of appetite and a general feeling of weakness. If you have a serious infection, either before starting treatment with Skilarence or during treatment, your doctor may advise you not to take Skilarence until the infection has resolved.

Gastrointestinal disorders
Tell your doctor if you have or have had problems with your stomach or intestines. Your doctor will advise you on what care you need to take during Skilarence treatment.

**Children and adolescents**
Children and adolescents below the age of 18 years should not take this medicine because it has not been studied in this age group.

**Other medicines and Skilarence**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking the following:

- **Dimethyl fumarate or other fumarates.** The active ingredient in Skilarence, dimethyl fumarate, is also used in other medicines such as tablets, ointments and baths. You must avoid using other products that contain fumarates to prevent taking too much.
- **Other medicines used to treat psoriasis,** such as methotrexate, retinoids, psoralens, ciclosporin, or other immunosuppressants or cytostatics (medicines that affect the immune system). Taking these medicines with Skilarence could increase the risk of side effects on your immune system.
- **Other medicines that can affect your kidney function,** such as methotrexate or ciclosporin (used to treat psoriasis), aminoglycosides (used to treat infections), diuretics (which increase urine), nonsteroidal anti-inflammatory drugs (used to treat pain) or lithium (used for bipolar disease and depression). These medicines taken together with Skilarence could increase the risk of side effects on your kidneys.

If you get severe or prolonged diarrhoea with Skilarence, other medicines may not work as well as they should. Talk to your doctor if you have bad diarrhoea and are concerned that other medicines you are taking might not work. In particular, if you are taking a contraceptive medicine (the pill), the effect may be reduced and you may need to use other barrier methods to prevent pregnancy. See the instructions in the patient leaflet of the contraceptive you are taking.

If you need a vaccination, talk to your doctor. Certain types of vaccines (live vaccines) may cause infection if used during treatment with Skilarence. Your doctor can advise you what would be best.

**Skilarence with alcohol**
Avoid strong alcoholic drinks (more than 50 ml of spirits containing more than 30% alcohol by volume) during treatment with Skilarence, as alcohol can interact with this medicine. This could cause stomach and intestinal problems.

**Pregnancy and breast-feeding**
Do not take Skilarence if you are pregnant or trying to become pregnant, as Skilarence may harm your baby. Use effective methods of contraception to avoid becoming pregnant during treatment with Skilarence (see also “Other medicines and Skilarence” above).
Do not breast-feed during treatment with Skilarence.

**Driving and using machines**
Skilarence may have a minor influence on the ability to drive and use machines. You may feel dizzy or tired after taking Skilarence. If you are affected, be careful when driving or using machines.

**Skilarence contains lactose**
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

**Skilarence contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

## 3. How to take Skilarence

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**Dose**
Your doctor will start your treatment with a low dose (using 30 mg Skilarence tablets). This helps to reduce stomach problems and other side effects. Your dose will be increased every week as shown in the table below (switching to 120 mg Skilarence tablets from week 4 onwards).

| Treatment week | Tablet strength | How many tablets to take during the day | | | Number of tablets per day | Total daily dose |
|---|---|---|---|---|---|---|
| | | Breakfast | Lunch | Evening meal | | |
| 1 | 30 mg | – | – | 1 | 1 | 30 mg |
| 2 | 30 mg | 1 | – | 1 | 2 | 60 mg |
| 3 | 30 mg | 1 | 1 | 1 | 3 | 90 mg |
| 4 | 120 mg | – | – | 1 | 1 | 120 mg |
| 5 | 120 mg | 1 | – | 1 | 2 | 240 mg |
| 6 | 120 mg | 1 | 1 | 1 | 3 | 360 mg |
| 7 | 120 mg | 1 | 1 | 2 | 4 | 480 mg |
| 8 | 120 mg | 2 | 1 | 2 | 5 | 600 mg |
| 9+ | 120 mg | 2 | 2 | 2 | 6 | 720 mg |

Your doctor will check how well your condition is improving after you start taking Skilarence and will check for side effects. If you have severe side effects after an increase in dose, your doctor may recommend that you temporarily go back to the last dose. If the side effects are not troublesome, your dose will be increased until your condition is well controlled. You may not need the maximum dose of 720 mg per day. After your condition has improved sufficiently, your doctor will consider how to gradually reduce the daily dose of Skilarence to what you need to maintain your improvement.

**Method of administration**
Swallow Skilarence tablets whole with liquid. Take your tablets during or immediately after a meal. Do not crush, break, dissolve or chew your tablets, as they have a special coating to help prevent irritation of your stomach.

**If you take more Skilarence than you should**
If you think you have taken too many Skilarence tablets, talk to your doctor or pharmacist.

**If you forget to take Skilarence**
Do not take a double dose to make up for a forgotten dose. Take the next dose at the usual time and continue taking the medicine exactly as described in this leaflet or exactly as agreed with your doctor. Please ask your doctor or pharmacist if you are not sure.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these side effects, such as reddening of the face or body (flushing), diarrhoea, stomach problems and nausea usually improve as you continue treatment.

The most serious side effects that may occur with Skilarence are allergic or hypersensitivity reactions; kidney failure or a kidney disease called Fanconi syndrome; or a severe brain infection called progressive multifocal leukoencephalopathy (PML). It is not known how commonly they occur. For symptoms see below.

Allergic or hypersensitivity reactions
Allergic or hypersensitivity reactions are rare but may be very serious. Reddening of the face or body (flushing) is a very common side effect which may affect more than 1 in 10 people. However, if you become flushed and get any of the following signs:
- wheezing, difficulty breathing or shortness of breath,
- swelling of the face, lips, mouth or tongue

stop taking Skilarence and call a doctor straight away.

Brain infection called PML
Progressive multifocal leukoencephalopathy (PML) is a rare but serious brain infection that can lead to severe disability or death. If you notice new or worsening weakness on one side of the body; clumsiness; changes in vision, thinking or memory; confusion; or personality changes lasting several days, stop taking Skilarence and talk to your doctor straight away.

Fanconi syndrome
Fanconi syndrome is a rare but serious kidney disorder which may occur with Skilarence. If you notice you are passing more urine, are more thirsty and drinking more than normal, your muscles seem weaker, you break a bone, or just have aches and pains, talk to your doctor as soon as possible so that this can be investigated further.

Talk to your doctor if you get any of the following side effects.

Very common side effects (may affect more than 1 in 10 people):
- decrease in white blood cells called lymphocytes (lymphopenia)
- decrease in all white blood cells (leukopenia)
- reddening of the face or body (flushing)
- diarrhoea
- bloating, stomach pain or stomach cramps
- feeling sick (nausea)

Common side effects (may affect up to 1 in 10 people):
- increase in all white blood cells (leukocytosis)
- increase in specific white blood cells called eosinophils
- increase in certain enzymes in the blood (used for checking the health of your liver)
- being sick

- constipation
- gas (flatulence), stomach discomfort, indigestion
- decreased appetite
- headache
- feeling tired
- weakness
- feeling hot
- abnormal sensations of the skin, such as itching, burning, stinging, tickling or tingling
- pink or red blotches on the skin (erythema)

Uncommon side effects (may affect up to 1 in 100 people):
- dizziness
- excess protein in the urine (proteinuria)
- increase in serum creatinine (a substance in the blood used for measuring how well your kidneys are working)

Rare side effects (may affect up to 1 in 1,000 people):
- allergic skin reaction

Very rare side effects (may affect up to 1 in 10,000 people):
- acute lymphatic leukaemia (a type of blood cancer)
- decrease in all types of blood cells (pancytopenia)

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Skilarence

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Skilarence 120 mg contains**
- the active substance is dimethyl fumarate. One tablet contains 120 mg dimethyl fumarate.
- the other ingredients are: lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, methacrylic acid-ethyl acrylate copolymer (1:1), talc, triethyl citrate, titanium dioxide (E171), simethicone, indigo carmine (E132) and sodium hydroxide.

**What Skilarence 120 mg looks like and contents of the pack**
Skilarence 120 mg is a blue, round tablet with a diameter of approximately 11.6 mm.
Pack sizes: 40, 70, 90, 100, 120, 180, 200, 240, 300, 360 and 400 gastro-resistant tablets. Not all pack sizes may be marketed. The tablets are packed in PVC/PVDC-aluminium blisters.

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**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.