SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Skilarence 30 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 30 mg dimethyl fumarate.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet

White, film-coated, round, biconvex tablet with a diameter of approximately 6.8 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 of Skilarence, it is recommended to begin treatment

with a low initial dose with subsequent gradual increases. In the first week, a 30 mg dose is taken once daily (1 tablet in the evening). In the second week, a 30 mg dose is taken twice daily (1 tablet in the morning and 1 in the evening). In the third week, a 30 mg dose 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 a 120 mg dose in the evening. This dose is then increased by one 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 (six 120 mg tablets).

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.

Dose 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 children below the age of 18 years have not been established. There are no data available with Skilarence in paediatric population.

Method of administration

For oral use.
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, 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 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 should only be initiated once the infection has resolved. If a patient develops an infection during treatment, suspension of treatment should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Patients receiving this medicinal product 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 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. It 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 treatment and by taking the gastro-resistant tablet(s) with food (see sections 4.2 and 4.8).

Renal function

During the Phase III placebo-controlled clinical study, 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 dose 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) (see section 4.8). 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 (see section 4.8). 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 (see section 4.2).

Flushing

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

Excipients

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

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, simultaneous use of other fumaric acid derivatives (topical or systemic) should be avoided.

Concurrent therapy with nephrotoxic substances (e.g. methotrexate,

ciclosporin, aminoglycosides, diuretics, non-steroidal anti-inflammatory drugs (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 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. Additional contraceptive methods in case of stomach and intestinal problems that could reduce the effectiveness of oral contraceptives could 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

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 are gastrointestinal events followed by flushing and lymphopenia.

Tabulated list of adverse reactions

The following is a list of adverse reactions experienced by patients treated with Skilarence during the clinical development, post-marketing experience 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**
Infections and infestations	Herpes zoster	Not known**
Blood and lymphatic system disorders	Lymphopenia Leukopenia Eosinophilia Leukocytosis Acute lymphatic leukaemia* Irreversible pancytopenia*	Very common Very common Common Common Very rare Very rare
Metabolism and nutrition disorders	Decreased appetite	Common
Nervous system disorders	Headache Paraesthesia Dizziness* Progressive multifocal leukoencephalopathy	Common Common Uncommon Not known
Vascular disorders	Flushing	Very common
Gastrointestinal disorders	Diarrhoea Abdominal distension Abdominal pain Nausea Vomiting Dyspepsia Constipation	Very common Very common Very common Very common Common Common Common

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

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

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).
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.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: Immunosuppressants, other immunosuppressants, ATC code: L04AX07

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 dose was necessary and the dose was to be steadily reduced to an individual maintenance dose. In case of individual intolerability of the increased dose 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).

Maintenance of efficacy has been observed during long-term treatment with dimethyl fumarate-containing products. 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.

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 psoriasis (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 data reveal no special hazard for humans based on conventional studies of safety pharmacology and genotoxicity.

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

Core
Lactose monohydrate
Cellulose microcrystalline
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

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

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

42, 70 and 210 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 NUMBER(S)

PLGB 16973/0040

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/2022

10 DATE OF REVISION OF THE TEXT

03/10/2024