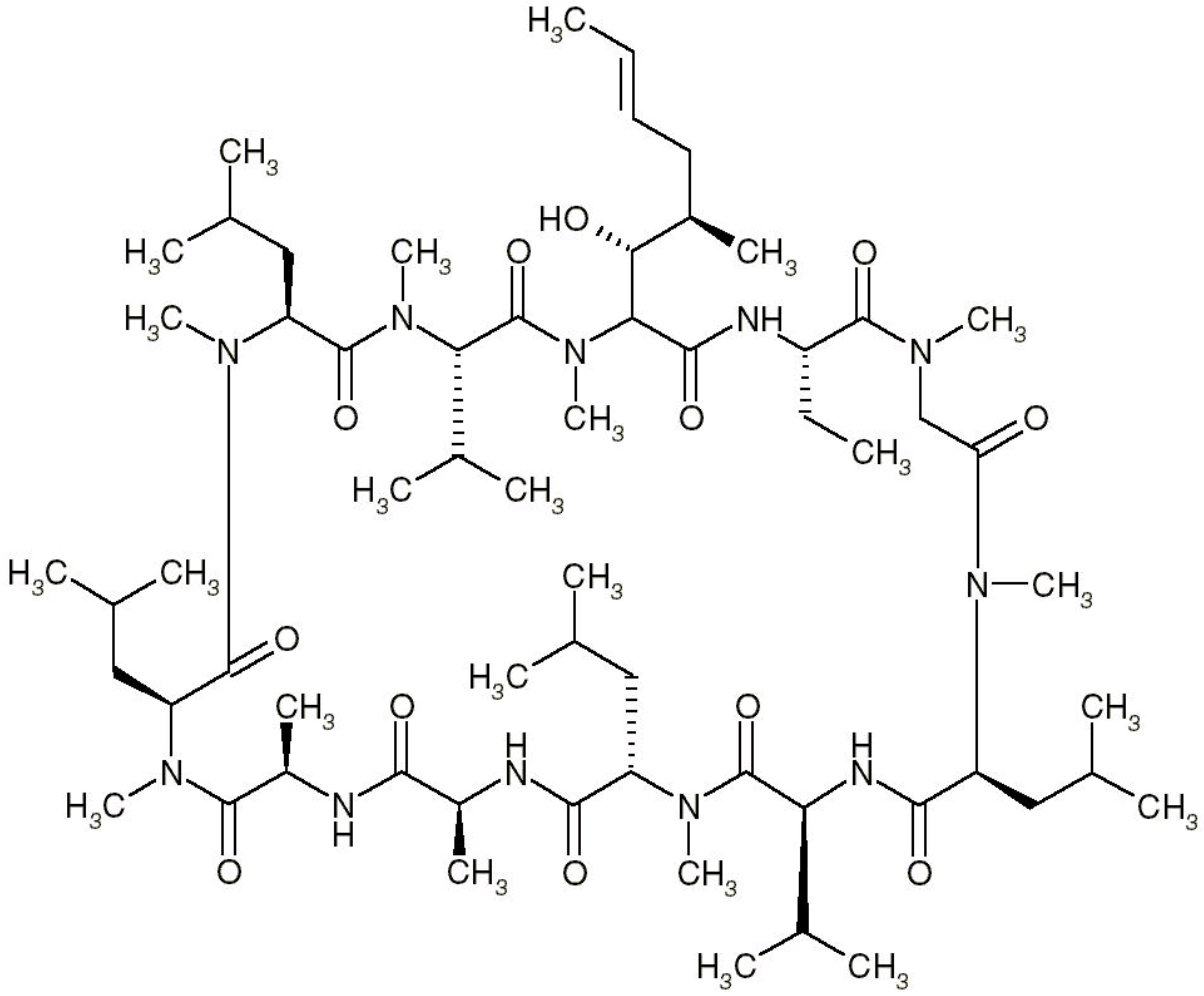
Guideline
Off-label drug use in dermatology
The GRADE approach



Guideline title: Off-label drug use in dermatology

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This guideline is formulated by a working group of the Dutch Society of Dermatology and Venereology, which was installed for this purpose. Subsequently, the guideline was approved by the general assembly of the Society. The guideline represents the current professional standard at the time of the guideline was drawn up.

The guideline contains recommendations of a general character. It is possible that these recommendations are not applicable in an individual case. The suitability and application of the guideline in practice is the responsibility of the treating physician. Facts or circumstances may occur in which it may be advisable to deviate from the guideline in the interest of the patient.

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List of conflicts of interest
None reported

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I. GENERAL INTRODUCTION

Objective
A guideline is a document with recommendations to support patient care in daily practice. The guideline is based on results of searching scientific literature and subsequent consensus of the working group, aimed at deciding on the appropriate medical intervention. A guideline and the documents derived from it (e.g. patient information), give recommendations for the treatment of patients, including psychosocial care.

Intended users
The guideline is intended for medical professionals, including: dermatologists, general practitioners and pharmacists. A text derived from the guideline is available for patients.

Composition of the working group
A working group was appointed for the development of the guideline. This group consisted of dermatologists, researchers, pharmacists and a general practitioner from Lareb (the Dutch pharmacovigilance centre). During the formation of the group, the geographical distribution of its members was taken into account as well as a balanced representation of academic and non-academic employment. The members of the working group have acted independently and no conflict of interest has been reported.

Methodology of the working group
During a period 2 years the working group worked on a draft guideline. An expert group made a bottleneck analysis during the preparatory phase. The expert group compiled a list of drugs which are frequently subscribed for off-label use in dermatology. The listed drugs were prioritized according to frequency of use and occurrence of potential serious adverse events. The members of the working group had the opportunity to propose alterations in the list of selected drugs The members of the working group agreed on composing a guideline about the off-label use of the following selected drugs:

azathioprine
cyclosporin
methotrexate
sulfasalazine
dapsone
hydroxychloroquine
Fumarates (off-label use for indications other than psoriasis in Germany; for other countries unlicensed use)

The working group agreed that the outcomes efficacy/effectiveness and safety are crucial for decision making. The working group started by making a draft guideline for azathioprine and decided that the applied methods would serve as a blueprint for the other five drugs. Useful literature was found by systematic searches and by checking of references (see "Methodology of literature search"). The members of the working group assessed the relevant literature with regard to content and quality. Subsequently, conclusions were drawn and recommendations were made for off-label use of the selected drugs by the members of the working group. The final version of the guideline was approved by all scientific societies involved.

Methodology of literature search
Research question
For each selected drug a research question according to PICO was made.
PICO stands for:

- Participants/population: population of patients with a dermatological disease who are treated with a drug that is not registered for the use in this particular disease.
- Intervention: the selected drug.
- Comparison: any other treatment (e.g. other systemic therapy, placebo, quality of life intervention), in case of lack of a control group; no other treatment.

- Outcome: efficacy and/or safety.

Search strategy

For each selected drug a standardized search was performed in the Medline (by PubMed) (1950-October 2009), EMBASE (1980- October 2009) and CENTRAL (until October 2009) databases. This search strategy was designed by a literature specialist of the department 'Professionele Kwaliteit van de Orde van Medisch Specialisten'. Also, references of included articles were screened for eligibility.

Pre-exclusion with keywords

Since the goal of this guideline was to give an overview of off-label drug use, articles dealing with registered indications were excluded. After the searches were uploaded in Reference Manager, articles labeled with possible keywords for exclusion were selected. A sample was taken of these selected articles to check if there were any relevant articles in that selection. The sample size was either 20 or 50 articles, depending on the number of articles labeled with a specific keyword. If the sample didn't contain any relevant articles, all the articles labeled with a specific keyword were excluded.

In the searches of cyclosporin, methotrexate, dapsone, hydroxychloroquine and sulfasalazine articles with the keywords 'case report' were excluded after a sample of 50 articles didn't reveal any relevant articles for inclusion.

In addition, articles with the following keywords were excluded after a sample of 20 articles didn't show any relevant articles:

Cyclosporin	Dapsone
- Transplantation	- Leprosy
- Transplantation immunology	- Mycobarterium leprae
- Transplantation immunology [Physiology]	- Pneumocystis carinii
- Acute graft rejection [Complication]	- Toxoplasmosis
- Acute graft rejection [Diagnosis]	- Spider
- Acute graft rejection [Drug therapie]	Methotrexate*
- Acute graft versus host disease	- Psoriasis
- Bone Marrow Transplantation	- Reumathoid arthritis
- Breast cancer	- Leukemia
- Graft Survival	- Osteosarcoom
- Graft Recipient	- Lymphoma
- Kidney Graft	- Bladder
- Kidney Transplantation	- Breast Cancer
- Liver Transplantation	- Mycosis
- Proteinuria	- Multiple sclerosis
- Nephritis	- Colitis
- Irradiation	- Asthma
- Heart transplantation	- Cancer + skin + cutaneous
- Vitamin	Sulfasalazine
- Psoriasis	- Rheumatoid arthritis
Hydroxychloroquine:	- Arthritis
- Rheumatic disease	- Crohn
- Systemic lupus erythematosus	- Ulcerative colitis
- Discoid lupus erythematosus	
- Lupus erythematosus	
* In the methotrexate search articles with the note 'review' were excluded after a sample of 20 articles didn't contain any relevant articles.	

An overall validation of this method was provided by the double search strategy. An initial/broad search (thus without using keywords) was compared with the search that used specific keywords for exclusion. Articles with the keywords 'case report', 'polymyositis' and 'idiopatic thrombocytopenic purpura' were excluded after a sample showed no relevant articles.
We found that all studies that were included in the initial/broad search were present in the search using keywords for exclusion. This validates the method of excluding articles by using keywords.

Selection of articles
All articles with title and abstract referring to off-label treatment with the predefined drug in patients with dermatological diseases were selected.

In- and exclusion criteria
Selection of the articles was performed by using the following pre-defined in- and exclusion criteria.
Inclusion criteria:

- The article concerns the selected drug and
- The selected drug is used in the treatment of a dermatological disease for which that particular drug is not registered in the Netherlands (up to date until 01-10-2009).

Exclusion criteria:

- Case reports with less than 5 subjects*
- Lack of data on safety and efficacy
- Articles concerning treatment other than systemic treatment with the selected drug
- Animal studies
- In vitro studies
- Double publications
- Articles concerning diseases that are primarily treated by other specialists
- Language other than English, French, German and Dutch

No restrictions were imposed regarding age, gender, skin type and number of subjects in a study and date of publication.
* A random sample of the excluded articles was taken to check if any relevant adverse events were missed.

Data extraction
Of all the included articles, data were extracted by two independent reviewers. This was done by using a standardized data extraction form. Discrepancies were discussed until agreement was reached.
Data- extraction was performed on:

- Methodological quality
- Study characteristics
- Efficacy/Effectiveness
- Safety

Methodological quality
Randomized controlled trials (RCT's) were assessed following the criterion grading system described in the *Cochrane Handbook for systematic reviews of interventions 5.0.0* (updated February 2008). To assess the risk of bias within included RCT's, the following parameters for methodological quality were used; sequence generation, concealment of allocation, blinding (of participants, researchers and outcome assessment), reporting of incomplete data, presence of selective outcome reporting and other potential threats to validity.

The methodological quality of cohort studies was assessed by using the checklists for cohort studies described by the Dutch Cochrane Centre.

Demographics
Data of demographics were extracted concerning:

- Study design: randomized? controlled? prospective, retrospective?
- Treatment arms
- Disease of the subjects: severity, stage, subtype, duration
- Previous medications
- Diagnostics: what was the method of diagnosis? Clinical, histopathological, other diagnostic criteria?
- Subjects: number, male/female, age, subgroups (e.g. age, ethnic origin)
- Duration of treatment
- Duration of follow up
- Concomitant medication
- Dosing schedule of the selected drug

Efficacy/effectiveness

- Used outcome parameters: clinical assessment, global assessment, quality of life measurement, laboratory markers, onset of effect, duration of remission, relapse rate, etc.
- Severity outcomes: the result of the used outcome parameters. Differences between baseline and end of the study and between treatment groups.

Safety
Safety is an important issue in off-label use of medication. The working group scored all adverse events, including a special focus on serious adverse effects. Within the included studies, every study that reported (serious) adverse events was taken into account. Adverse events reported in RCT's or cohorts will be compared with the adverse events that occurred in the control group. If possible a relative risk will be calculated.

Extracted safety data:

- Adverse events: which? how many? at what time during treatment or after treatment?
- Serious adverse events: which? how many? at what time during treatment or after treatment?
- Withdrawals due to adverse events?

An Adverse Event (AE) was defined as an unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless whether it is considered related to the medical treatment or procedure that occurs during the course of the study.

A Serious Adverse Events (SAE) was defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is reported in the study as such.

Handling of the data
Extracted data will be presented in tables and with accompanying text per disease following standardized means.

Level of evidence
The description and assessment of the articles according to the data extraction (see above) are listed in separate sections under the headers "Safety data off -label Fumarates" or "Efficacy/effectiveness data off-label Fumarates" and in tables (see section Tables).

Not all data extracted from articles are equally valuable. Therefore, for each disease, the included articles are summarised and a conclusion is generated, in which the level of the evidence is indicated according to the GRADE system (see boxes below). Consequently the recommendations in this guideline are based on evidence generated by scientific research, with emphasis on the outcomes safety and effectiveness/efficacy. The search results that were used are up to date until at least 01-10-2009, unless stated otherwise.

GRADE system	
Type of evidence	Randomized trial = high Observational study = low Any other evidence = very low
Decrease* grade if	• Important inconsistency • Some or major uncertainty about directness • Imprecise or sparse data • High probability of reporting bias • Serious or very serious limitation to study quality
Increase grade if	• Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) • Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2) • Evidence of a dose response gradient (+1) • All plausible confounders would have reduced the effect (+1)
*Each quality criterion can reduce the quality by one or, if very serious, by two levels.	

Conclusion

- High = further research is very unlikely to change our confidence in the estimate of effect
- Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low = any estimate of effect is very uncertain.

Development of the recommendations

For the development of a recommendation, other aspects than scientific evidence are also of importance, such as: patient preferences, availability of special techniques or expertise, organisational aspects, social consequences or costs. Known adverse events mentioned in the summary of product characteristics (SPC) are also taken into account, as far as they were not already distilled from the included scientific literature (for example known from label use evidence). These aspects are discussed after the conclusion(s). On the basis of literature, the conclusion is here placed in the context of daily practice, and the pros and cons of the various treatments are balanced against each other. The final formulated recommendation is the result of the available evidence in combination with these considerations and can be formulated as a weak or strong recommendation in favour of a certain therapy or as a weak or strong recommendation against a certain therapy (see box below). The aim of this procedure and the formulation of the guideline using this 'format' is to enhance the transparency of the guideline.

Recommendation

- Strong = if clinicians, based on the available evidence, are very certain that benefits do, or do not, outweigh risks or burdens, they will make a strong recommendation.
- Weak = if clinicians, based on the available evidence, believe that benefits and risks or burdens are finely balanced, or if considerable uncertainty exists about the magnitude of benefits and risks, they must make a weak recommendation.

Implementation and evaluation

During the various phases of developing of the draft guideline, the implementation of the guideline and the actual workability of the recommendations are taken into account as much as possible. The guideline is presented at national meetings, distributed to all relevant professional groups and hospitals through the internet and in various medical journals attention will be given to the guideline.

Legal significance of guidelines

Guidelines are not legal regulations, but scientifically and broadly based insights and recommendations which medical professionals should meet in order to provide qualitatively good medical care. Since guidelines assume dealing with 'average patients', medical professionals can deviate in individual cases from the guidelines when necessary. Deviation from the guideline – if required by the situation of the patient – is sometimes even imperative. However, intentional deviation from the guideline should be explained and documented in the medical record and, when necessary, with consent of the patient. . Article 68 of the Dutch Medicines Act of juli 1st 2007 states the following about off-label drug prescription: 'Prescribtion of drugs outside of the registered indications of the Board is only licit when this is supported by guidelines and protocols developed by the profession. When the guidelines and protocols are still in the developmental stage, consultation between the attending physician and the pharmacist is required.' (Original text: *'Het buiten de door het College geregistreerde indicaties voorschrijven van geneesmiddelen is alleen geoorloofd wanneer daarover binnen de beroepsgroep protocollen of standaarden zijn ontwikkeld. Als de protocollen of standaarden nog in ontwikkeling zijn, is overleg tussen de behandelend arts en de apotheker noodzakelijk.'*)

Guideline validation

The guideline was authorised by:

- Dutch Society of Dermatology and Venereology (NVDV)
- Royal Dutch Association for the Advancement of Pharmacy (KNMP)
- Dutch Association of Hospital Pharmacists (NVZA)

Guideline maintenance

A guideline can only be leading, if it is maintained on a continuous base, with systematic monitoring of medical scientific literature as well as regular contributions from clinical practice..In case of important developments, it can be decided that the complete working group shall meet to propose amendments, which will be distributed among the various professional groups. A revision will be planned at least every five years.

II. FUMARATES

Introduction

Fumarates, which are ester derivatives of fumaric acid, are small molecules with immunomodulating properties (Mrowietz and Asadullah 2005). Fumarates were first described as an oral anti-psoriatic treatment by the German chemist Schweckendick in 1959 (Schweckendiek 1959). The treatment with fumarates was developed further in the 1970s and 1980s in Switzerland (Schafer 1984). The first randomized clinical trials with oral fumarates were published in the early 1990s, and in 1994 treatment with fumarates became approved in Germany for the treatment of adult patients with severe psoriasis. Fourteen years later, in 2008, the approved indication of fumarates was extended to include patients with moderate psoriasis (Mrowietz, Rostami-Yazdi et al. 2009). The licensed fumarates-formulation in Germany is Fumaderm (Biogen Idec GmbH, Ismaning, Germany), which consists of a mixture of the fumarates dimethylfumarate (DMF) and monoethylfumarate (MEF) in two strengths: Fumaderm initial 105 mg tablets containing 30 mg DMF and 75 mg MEF, and Fumaderm 215 mg tablets containing 120 mg DMF and 95 mg MEF. Fumaderm is dosed according to a standardized incremental dosage regimen up to Fumaderm 215 mg six times a day (Pathirana, Ormerod et al. 2009). To date, Fumaderm is one of the most prescribed systemic treatments for psoriasis in Germany (Mrowietz, Adamczyk et al. 2011). In other European countries like the Netherlands and the United Kingdom, the use of fumarates for the treatment of moderate to severe psoriasis has been increasingly reported, although its use in these countries remains unlicensed. In the Netherlands fumarates are not approved, but regarded and reimbursed as a rational pharmacotherapy for psoriasis (Health Care Insurance Board, 2004).

The mechanism of action by which fumarates improve psoriasis is only partially understood. Currently, the major mechanism of action is thought to be the interaction between DMF and intracellular glutathione leading to inhibition of nuclear factor kappa B (NF-kB)-mediated transcription of pro-inflammatory mediators and of adhesion molecules. Other mechanisms of DMF are linked to impairing dendritic cell maturation, to shifting cytokine production by T helper cells, and to the induction of apoptosis (Pathirana, Ormerod et al. 2009). Experimental in vitro studies indicate that DMF and not MEF is most likely the active fumarates-component of Fumaderm (Lehmann, Listopad et al. 2007). In addition, a small randomized controlled trial among 45 psoriasis patients reported that the clinical efficacy of DMF alone is not significantly different from that of DMF with MEF (Nieboer, de Hoop et al. 1990). Furthermore, pharmacokinetic studies in psoriasis patients showed that after oral administration of fumarates only monomethylfumarate (MMF) is detectable in serum, suggesting that MMF is the active metabolite of DMF (Litjens, Burggraaf et al. 2004).

The long-term safety profile of fumarates is favourable as an increased risk of infections and malignancies have not been described so far in patients treated with fumarates continuously for over 10 years (Hoefnagel, Thio et al. 2003; Pathirana, Ormerod et al. 2009; Wain, Darling et al. 2010). However, inconvenient adverse events as gastrointestinal complaints and skin flushing occurring in the beginning of fumarates treatment lead in about 30 to 40% to treatment discontinuation. Several approaches have been undertaken or suggested to bypass this limiting factor for continuing fumarates. First, a decrease of gastrointestinal complaints is achieved by using enteric-coated tablets. Second, fumarates-formulations containing solely DMF without MEF may be associated with less adverse events (Ogilvie, Lewis Jones et al. 2011). Finally, slow-release formulations of fumarates may decrease further the incidence of adverse events (Kunst 1998).

Although fumarates were initially developed for the systemic treatment of psoriasis, there are now an increasing number of reports of beneficial effects of fumarates for several inflammatory and granulomatous skin diseases such as cutaneous sarcoidosis, necrobiosis lipodica, granuloma annulare, and lichen planus (Breuer, Gutzmer et al. 2005; Klein, Coras et al. 2012). However, fumarates are not limited to treatment of dermatological diseases. A DMF-formulation (BG-12) was effective in the treatment of multiple sclerosis in two phase 3 clinical trials (Fox, Miller et al. 2012; Gold, Kappos et al. 2012), while fumarates are currently tested in pre-clinical studies for a variety of diseases (Meissner, Valesky et al. 2012).

Research question
What is the safety and efficacy of oral treatment with fumarates in patients with dermatological diseases?

Methods literature search
There was no limit with respect to the date of the publication. Literature references of all relevant articles found were checked in order to find additional articles. In addition, data published in Micromedex concerning Fumarates were studied to retrieve further potential relevant references regarding safety in off-label use. None were found.

Study selection and data extraction
All articles with title and abstract referring to treatment with fumarates of patients with dermatological diseases were selected by two reviewers. Next, to determine eligibility, the full text of the selected articles was screened by two reviewers. Disagreements were solved by discussion. Predefined in- and exclusion criteria are described in detail in the introduction section. Data on methodological quality, demographics, efficacy and safety were extracted by two independent reviewers using a data extraction form. Disagreements about data extraction were solved by discussion.

General treatment considerations

Nota bene!

The text in this section is based on the Dutch guideline on psoriasis of the Dutch Society of Dermatology and Venereology, which was last updated on 28-10-2011. The text was modified by the working group to reflect the best practice in the Netherlands at the time the guideline was made. Modifications are depicted in a grey box. It is advisable to consider the recommendations when prescribing Fumarates, however the text is not intended as a substitute for the complete text of the guideline. The complete and up to date text of the Dutch guideline on psoriasis is available on www.nvdv.nl.

Dosage of fumarates

- In general, a standardized incremental dosage schedule is applied, in which the starting dosage per day is 105 mg of fumarates (30 mg DMF and 75 mg MEF). At week 8 of the dosage schedule the clinical response can be evaluated, after which point the dosage of 480 mg can be maintanted when having reached at least a PASI-50 response, or after which point the dosage can be further increased up to 720 mg in case of an insufficient response.
- The highest induction dosage of fumarates should be maintained until reaching complete remission of the psoriasis.
- Afterwards, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the maintenance of that response. Most patients require a daily maintenance dosage of 240-360 mg of fumarates.
- If no improvement occurs within 12 weeks of treatment, consideration should be given to withdrawing fumarates.
- No specific schedule for withdrawing fumarates is required, considering that rebound phenomona or exacerbations of psoriasis following withdrawing of fumarates have not been described.

Use in children
There is limited experience of fumarates in pediatric patients.There are only three case-reports published describing the effectiveness and safety of fumarates in children. Effectiveness and short-term safety were similar to that seen in adult psoriasis patients.

Contraindications
Treatment with fumarates is contra-indicated in patients with severe renal and/or hepatic insufficiency, gastrointestinal diseases, and hematological malignancies. Fumarates therapy should not be initiated in patients who may be pregnant, patients who are likely to become pregnant, or patients who are breastfeeding. Relative contra-indications are hematological disorders, and concomittant use of drugs with

known nephrotoxic potential.

Monitoring
Fumarates treatment should be regularly monitored with laboratory testing of blood count, liver enzymes, serum creatinine, serum cholesterol, urine sediment, proteinuria, and a pregnancy test. It is recommented to perform these tests before start of treatment and montly during the first 3 months of treatment. Thereafter, once every three months, and after 1 year of treatment once every 6 months.

Interaction with other drugs and other forms of interaction
To date, there is limited information available on interactions of fumarates with other drugs.

Use in Pregnancy and Lactation
Fumarates should not be given to patients who are pregnant or likely to become pregnant. Treatment with fumarates is not recommended during lactation.

Undesirable effects
There is no modern clinical documentation that can be used for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication. The following convention has been utilised for the classification of frequency: Very common, ≥ 1/10; common, ≥ 1/100 and < 1/10; uncommon, ≥ 1/1000 and < 1/100; rare, ≥ 1/10000 and < 1/1000; very rare, < 1/10000.

The most frequently occuring undesirable effects associated with fumarates are flushing and gastrointestinal complaints, occuring in up to 60% of the patients and mostly during the first months of treatment. Flushing may present with feelings of warmth, reddening of the face, and headaches that can occur for several minutes to several hours. Gastrointestinal complaints include diarrhoea, increased stool frequency, nausea, and abdominal cramps. A minority of patients experience pruritus or fatigue during fumarates treatment.

Several laboratory changes can occur during fumarates treatment, which include leucocytopenia, lymphocytopenia, eosinophilia, increase in cholesterol, increase in liverenzymes, and proteinuria.

There have been several cases described of renal toxicity associated with Fumarates.

Summary of registered adverse events	
Occurrence Events	Undesirable effect
Blood and lymphatic disorders	
Common	Lymphocytopenia, eosinophilia
Gastrointestinal disorders	
Very common: Common: Rare:	Diarrhoea Abdomincal cramps, flatulance Nausea,
Hepato-biliary disorders	
Rare:	Increase of liverenzymes
Very rare:	Isolated increase of ALAT, isolated increase of bilirubin.
Urinary	
Rare:	Proteinuria, increase of creatinin

Skin and subcutaneous tissue disorders	
Very common	Flushing
General symptoms	
Rare:	Headache, fatigue

Safety data of fumarates

The safety data described here are derived from all the identified studies reporting about safety (see section 'Methodology' for more information. The individual studies and tables can be found in section IV: Tables.

Adverse events

Occurance event	Adverse events without SAE (total number of patients = 2396)
Urinary tract	
	Proteinuria (13) Renal colics (1) Albuminuria (2) Impairment of renal function (1) Increase of creatinin (62) Microscopic haematuria (2) Urine casts (2)
Blood and lymphatic disorders	
	Lymphocytopenia (659), leucopenia (149), eosinophilia (146), Increase of protrombin time (2)
Gastrointestinal disorders	
	Gastro-intestinal complaints (645)
Hepato-biliary disorders	
	Elevation of liver enzymes (193)
Skin and subcutaneous tissue disorders	
	Pruritus (12) Local irritation/allergic reaction (3) Skin burning (2) Folliculitis (1) Rash (1) Hair loss (2)
Circulatory disorders	
	Hypertension (6) Palpitations (2)
Other	
	Flushing (356) Headache (18) Dizziness (12) Increased cholesterol (11) Fatigue (42) Loss of concentration (1) Increased sweating (1) Heat sensation (3) General malaise (18)

	Hyperglycaemia (6) Fever (1) Increase in body weight (3) Burning eyes (2) Loss of appetite (2) Decrease in body weight (1) Hyperpotassemia (8) Mental depression (1) Metallic taste (1) Feeling cold (1) Swollen leggs (1)` Feeling hot (1)
The following classification has been utilised for the classification of frequency: Very common, ≥ 1/10; common, ≥ 1/100 and < 1/10; uncommon, ≥ 1/1000 and < 1/100; rare, ≥ 1/10000 and < 1/1000; very rare, < 1/10000.	

Serious adverse events

- *Psoriasis*

Seven serious adverse events were described which occurred during treatment for psoriasis with fumarates. There were three serious adverse events related to renal insufficiency, and 1 related to glomerunonephritis. Two malignanies occurred during treatment with fumarates: 1 case of mammacarcinoma, and 1 case of a small well-differentiated squamous cell carcinoma. The other serious adverse event was related to an adnexitis.

Serious adverse events	
Occurrence Event?	Serious adverse events (total number of patients = 7)
Neoplasms benign and malignant (including cysts and polyps)	
	Mammacarcinoma (1) Small well-differentiated squamous cell carcinoma (1)
Renal disorders	
Uncommon:	Renal insufficiency (3) Glomerulonephritis (1)
Other	
Uncommon:	Adnexitis (1)

Evidence on safety derived from included RCT's

Conclusion on the strength of evidence concerning overall safety

Low	There is important inconsistency in the way that safety issues are addressed and (serious) adverse events are reported. There is also a considerable amount of indirectness and probability of reporting bias. The remaining body of evidence, consisting of other fundamental study designs (case series and cohort studies) do not deliver the strong evidence needed to increase the grade.

Considerations working group

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Efficacy/effectiveness data fumarates

Alopecia areata

Introduction
In total, 1 study published in 2006, was found in the literature in which patients with alopecia areata were treated with fumarates. This study was a prospective case series.
Effectiveness was measured by the number of patients with a response on fumarates therapy. Response was defined as: very good response with complete regrowth of the hair; good response with up to 50% regrowth of the hair; slight response with 25%-50% regrowth of the hair; little response with up to 25% regrowth of the hair; and no response with no regrowth of the hair.

Case series

Demography
This case series included 10 patients with alopecia areata, who were diagnosed with alopecia areata for at least 6 months and who had previously underwent three or more conventional therapies without clinical response. The age of the subjects ranged from 17 to 44 years. Mean duration of alopecia areata was 50.1 months. The fumarates dosage employed varied: 2 patients were treated with Fumaderm 215 mg thrice a day, 1 patient with Fumaderm 215 mg 5 times a day, and 7 patients with Fumaderm 215 mg six times a day. The duration of treatment was 6 months and there was no follow-up period. There were no drop outs during the study.

Effectiveness
After six months of treatment with fumarates 6 out of 10 patients showed positive results. Three patients had very good results with an almost complete remission, and 1 patient had a good response, showing a focal remission. Two patients had little to moderate responses with diffuse growth of thin hair. Four patients showed no regrowth of hair in the area of focus.

Conclusion on strength of evidence for efficacy of fumarates in alopecia areata

Very Low	The available study was of very low quality with sparse data and uncertainty about directness.

Magnitude of treatment effect

Very uncertain estimate for a moderate effect

Clinical recommendation for alopecia areata

Weak	There is a weak recommendation for treating alopecia areata with fumarates. It is uncertain if the beneficial effects outweigh the safety aspects.

Remarks on clinical recommendation for alopecia areata

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	- One study has demonstrated some effect of fumarates in patients with alopecia areata. Uncertain estimate. - Uncertainty about the safety of fumarates. - Costs may vary with the number of follow-up visits and dosage of fumarates.
Importance of the outcome that treatment prevents	- Complete regrowth of hair.

Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	- Moderate
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- Only descriptive outcomes. Very uncertain.
Risks associated with therapy	- Side effects of fumarates
Burdens of Therapy	- See risks. Daily oral administration of tablets. Frequent laboratory testing on blood and urine samples
Risk of target event	- Target event is alopecia areata; so risk is 100%.
Costs	- Costs of fumarates are € 30,32 for 7 days 1dd 720 mg, not included are the costs for delivery, laboratory monitoring, and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Large varying values between patients
Other	-There are other treatment options available.

References

Venten I, Hess N, Hirschmüller A, Altmeyer P, Brockmeyer N. Treatment of therapy-resistant Alopecia areata with fumaric acid esters. Eur J Med Res. 2006 Jul 31;11(7):300-5.

Cheilitis granulomatosa

Introduction
In total, 1 study published in 2007, was found in the literature in which patients with cheilitis granulomatosa were treated with fumarates. This was a prospective case series.
Effectiveness was measured by the number of patients with a complete remission or a marked reduction of swelling of the lip. Also, the time to remission and duration of remission were used to assess effectiveness.

Case series
Demography
Jansen et al. included 5 patients with cheilitis granulomatosa in their prospective case series. Diagnosis of cheilitis granulomatosa was histologically confirmed in all patients. The age of the subjects ranged from 25 to 56 years. Lip swelling was present for 5 to 18 months, with a mean duration of 11.6 months. Lingua plicata was found in 3 patients. Previous treatments were clofazimine, ketotifen and triamcinolon acetonide. Patients were treated with Fumaderm for 5 to 6 months (mean treatment duration 5.8 months). The maximum daily dose employed was Fumaderm 215 mg thrice a day. The follow-up period ranged from 4 to 8 months.

Effectiveness
After the treatment period with fumarates, significant reduction of lip swelling was achieved in 3 patients, while clearing of lip swelling could be observed in 2 patients. In all patients a rapid reduction of lip swelling was seen within the first week of treatment. There was no relapse within a mean follow-up period of 5.6 months (range 4-8 months). Lingua plicata remained unchanged in all 3 patients.

Conclusion on strength of evidence for efficacy of fumarates in cheilitis granulomatosa

Very Low	The available study was of very low quality with sparse data and very uncertainty about directness.

Magnitude of treatment effect

Very uncertain estimate for a good effect

Clinical recommendation for cheilitis granulomatosa

Weak	There is a weak recommendation for treating cheilitis granulomatosa with fumarates. It is uncertain if the beneficial effects outweigh the safety aspects.

Remarks on clinical recommendation for alopecia areata

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	- One study has demonstrated some effect of fumarates in patients with cheilitis granulomatosa. Uncertain estimate. - Uncertainty about the safety of fumarates. - Costs may vary with the number of follow-up visits and dosage of fumarates.
Importance of the outcome that treatment prevents	- Complete remission cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	- Good

Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Only descriptive outcomes. Very uncertain.
Risks associated with therapy	- Side effects of fumarates
Burdens of Therapy	- See risks. Daily oral administration of tablets. Frequent laboratory testing on blood and urine samples
Risk of target event	- Target event is cheilitis granulomatosa; so risk is 100%.
Costs	- Costs of fumarates are € 30,32 for 7 days 1dd 720 mg, not included are the costs for delivery, laboratory monitoring, and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Large varying values between patients
Other	- There are other treatment options available.

References

Jansen T. and Grabbe S. Treatment of cheilitis granulomatosa with fumaric add esters: Results of a prospective noncontrolled study. Aktuelle Dermatologie 2007 33:3 (72-75)

Cutaneous sarcoidosis

Introduction
One case series, published in 2005, was found in the literature in which patients with cutaneous sarcoidosis were treated with fumarates. This was a retrospective case series.
Effectiveness was measured by the number of patients with improvement of the skin lesions, which was defined as complete clearance, marked improvement, or slight to moderate improvement.

Case series
Demography
This case series included 8 patients with cutaneous sarcoidosis. The method of diagnosing sarcoidosis was not reported. The age of the subjects ranged from 34 to 67 years. Previous treatments used by the patients were chloroquine, azathioprine, allopurinol, clofazimine, dapsone, tetracycline, and topical and systemic corticosteroids.
Patients were treated with Fumaderm.The mean maximum daily dose employed varied from Fumaderm 215 mg once a day to Fumaderm 215 mg six times a day, which was individually determined based upon tolerance. The number of patients which used concomitant topical corticosteroids was unclear. Duration of treatment varied from <1 to >23 months, and duration of follow-up was not reported.

Effectiveness
One patient showed an excellent clinical response after which he discontinued fumarates. Within 1 month, however, the lesions recurred. Subsequently, therapy with fumarates was restarted, and the lesions disappeared again. Slight to moderate improvement was seen in 3 patients, whereas 4 patients showed no improvement. Of the 8 patients, 6 patients discontinued therapy due to adverse effects or due to lack of treatment. Two patients continued their fumarates therapy at time of data analysis.

Conclusion on strength of evidence for efficacy of fumarates in cutaneous sarcoidosis

Very Low	The only available study was of very low quality with small number of patients and uncertainty about directiveness.

Magnitude of treatment effect

Very uncertain estimate for a poor effect

Clinical recommendation for cutaneous sarcoidosis

Weak	There is a weak recommendation for treating cutaneous sarcoidosis with fumarates. It is uncertain if the beneficial effects outweigh the safety aspects.

Remarks on clinical recommendation for cutaneous sarcoidosis

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	- One study has demonstrated some effect of fumarates in cutaneous sarcoidosis patients. Very uncertain estimate. - Uncertainty about the safety of fumarates . - Costs may vary with the number of follow-up visits and dosage of fumarates .
Importance of the outcome that treatment prevents	- Complete remission of cutaneous lesions.
Magnitude of treatment effect*	- Moderate

* the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- Only descriptive outcomes
Risks associated with therapy	- Side effects of fumarates
Burdens of Therapy	- See risks. Daily oral administration of tablets. Frequent laboratory testing on blood and urine samples
Risk of target event	- Target event is cutaneous sarcoidosis; so risk is 100%.
Costs	- Costs of fumarates are € 30,32 for 7 days 1dd 720 mg, not included are the costs for delivery, laboratory monitoring, and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Moderate varying values between patients
Other	- There are other treatment options available.

References

Breuer K, Gutzmer R, Völker B, Kapp A, Werfel T. Therapy of noninfectious granulomatous skin diseases with fumaric acid esters. Br J Dermatol. 2005 Jun;152(6):1290-5.

Disseminated granuloma annulare

Introduction
In total, 3 case series published between 2005 and 2009 were found in the literature, in which patients with disseminated granuloma annulare were treated with fumarates.
Effectiveness was measured by the number of patients with improvement of the skin lesions, defined as 'complete clearance', 'marked improvement', 'slight to moderate improvement', or 'no improvement'. In the study of Eberlein-König et al. a visual analogue scale reaching from 0 to 120 was applied to assess the colour and the elevation of the skin lesions. In addition, time to remission, duration of remission, and time to relapse were used to assess effectiveness.

Case series
Demography
Three studies with case series were included concerning 29 patients with disseminated granuloma annulare. Diagnosis of disseminated granuloma annulare was clinically and histologically confirmed in the case series of Weber et al and of Breur et al. In the other study, the method of diagnosis was not reported. The age of the subjects ranged from 19 to 80 years. Previous treatments used by patients from the study of Weber et al. included phototherapy, retinoids, PUVA, and topical corticosteroids. Breuer et al. listed dapsone, tetracycline, PUVA, UVA-1, allopurinol, and topical corticosteroids as previous treatments, and in the study of Eberlein- König et al. precious treatments included topical corticosteroids, acupuncture, topical vitamin E, oral vitamin C, systemic corticosteroids, PUVA, and UVA-1 therapy.
Breuer et al. reported that some subjects might have used concomitant topical corticosteroids during fumarates treatment; in the other two studies the use of concomitant medication was not reported.
In all studies the dosage of fumarates was employed according to standardized incremental dosage regimen up to Fumaderm 215 mg six times a day. However, only in the study of Weber et al. the maximum dosage was increased up to Fumaderm 215 mg 2 times a day. The duration of treatment varied from 1 to 18 months, and in all studies the duration of follow-up was not reported.

Effectiveness
Weber et al. reported that fumarates significantly improved disseminated granuloma annulare in 5 of 8 patients, with 1 patient who achieved 'complete clearance' and 4 'marked improvement'. One patients had a 'slight to moderate improvement', while 2 patients had no improvement. The mean time to effect was 3.7 months with a range from 1 to 6 months. Duration of remission was not reported. Treatment with fumarates in the study of Eberlein-Köning et al. induced a significant clinical improvement in elevation and colour of skin lesions in 7 out of 8 patients, with complete remission in 3 patients and partial remission in 4 patients. Granuloma annulare remained unchanged in 1 patient. The first signs of amelioration were seen after the third week of therapy. The mean score of the visual analogue scale assessing the colour of the skin lesions decreased from 80.1 ± 15.1 to 50 ± 31.8 ($p<0.01$). Similarly, the mean score of elevation of the skin lesions decreased from 81.5 ± 23.2 to 37.75 ± 32.6 ($p<0.05$) on the visual analogue scale. Eberlein-könig et al. mentioned that patients with a complete remission were treated with higher doses Fumaderm 215 mg tablets (mean: 5.3 ± 1.2 tablets, range 4–6 tablets) than those with a partial remission (mean: 2.0 ± 1.2 tablets, range 1–3 tablets). In the case series of Weber et al. lower dosages of Fumaderm were used up to a maximum dose of Fumaderm 215 mg 2 times a day.
Breuer et al. reported 'cleared or marked improvement' in 2 patients, 'slight to moderate improvement' in 6 patients, and 'no beneficial effects in 5 patients. One patient discontinued fumarates after an excellent clinical response. Within three months the lesions recurred. Subsequently, therapy with fumarates was restarted and the lesions disappeared again. This patient was still taking fumarates at time of data closure.

Conclusion on strength of evidence for efficacy of fumarates in disseminated granuloma annulare

Very Low	The 3 available studies were of very low quality with sparse data and uncertainty about directness.

Magnitude of treatment effect

Uncertain estimate for a moderate effect

Clinical recommendation for disseminated granuloma annulare

Weak	There is a weak recommendation for treating disseminated granuloma annulare with fumarates. It is uncertain if the beneficial effects outweigh the safety aspects.

Remarks on clinical recommendation for alopecia areata

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	- One study has demonstrated some effect of fumarates in disseminated granuloma annulare patients. Uncertain estimate. - Uncertainty about the safety of fumarates. - Costs may vary with the number of follow-up visits and dosage of fumarates.
Importance of the outcome that treatment prevents	- Complete remission of cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	- Moderate
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- A visual analogue scale and descriptive outcomes. Uncertain.
Risks associated with therapy	- Side effects of fumarates
Burdens of Therapy	- See risks. Daily oral administration of tablets. Frequent laboratory testing on blood and urine samples
Risk of target event	- Target event is disseminated granuloma annulare; so risk is 100%.
Costs	- Costs of fumarates are € 30,32 for 7 days 1dd 720 mg, not included are the costs for delivery, laboratory monitoring, and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Moderate varying values between patients
Other	- There are other treatment options available.

References

- Breuer K, Gutzmer R, Völker B, Kapp A, Werfel T. Therapy of noninfectious granulomatous skin diseases with fumaric acid esters. Br J Dermatol. 2005 Jun;152(6):1290-5.
- Eberlein-König B, Mempel M, Stahlecker J, Forer I, Ring J, Abeck D. Disseminated granuloma annulare-treatment with fumaric acid esters. Dermatology. 2005;210(3):223-6.
- Weber HO, Borelli C, Röcken M, Schaller M. Treatment of disseminated granuloma annulare with low-dose fumaric acid. Acta Derm Venereol. 2009;89(3):295-8.

Necrobiosis lipoidica

Introduction
In total one case series, published in 2005, was found in the literature in which patients with necrobiosis lipoidica were treated with fumarates. This was a prospective case series.
Effectiveness was measured by a clinical score, defined on a 4-point scale of erythema, infiltration, ulceration, and pain. Also, the duration of remission and time to relapse were used to assess effectiveness. Other outcome tools used were dermal density as assessed by means of a 20-MHz ultrasound, and a histological score, which was defined with a 4-point scale of inflammatory infiltrate, collagen degeneration, and epithelioid histiocytes.

Case series
Demography
One study with case series was included concerning 18 patients with necrobiosis lipoidica. Diagnosis of inflammatory active necrobiosis lipoidica was characterized by any of the following criteria: clinical signs of inflammation, sensations of itch and dysaesthesia, enlargement of lesions, or appearance of new lesions within the last three months. The age of the subjects ranged from 19 to 82 years, with a mean age of 43 years. Mean duration of necrobiosis lipoidica was 8.7 years, with a range from 1 to 23 years. Previous treatments were psoralen plus ultraviolet A therapy, cryotherapy, topical steroids, oral steroids, and intralesional steroids.
Patients were treated with Fumaderm, which was dosed according to a standardized incremental dosage regimen. However, the maximum daily dosage was Fumaderm 215 mg 5 times a day . Duration of treatment varied from 6 to 15 months, with a mean of 7.7 months. The follow-up period varied from 6 to 15 months, with a mean of 9.3 months. Three subjects were lost to follow up.

Effectiveness
Kreuter et al. reported a statistically significant decrease in the mean clinical score from 7.4 (SD 1.8) at the beginning of fumarates treatment to a mean score of 2.5 (SD 1.3) at the end of the treatment (P<0.001; 95% CI of difference 4.12–6.01). The clinical improvement of necrobiosis lipoidica was accompanied by a significant increase of dermal density (19.1 (8.1) vs. 27.1 (10.1); P < 0.019; 95% CI -14.4 to - 1.57), and a significant reduction of the histological score (P = 0.011). The structure of the dermal collagen returned to almost normal dermal architecture, and the inflammatory infiltrate decreased markedly, resulting in a significant decrease in histological score from 5.7 (1.9) at baseline to 3.9 (1.8) after therapy (P = 0.011; 95% CI of difference 0.48–3.05). During a follow-up of at least 6 months, clinical outcome remained stable in all patients.

Conclusion on strength of evidence for efficacy of fumarates in necrobiosis lipoidica

Very Low	The only available study was of very low quality with sparse data and uncertainty about directness.

Magnitude of treatment effect

Very uncertain estimate for a good effect

Clinical recommendation for necrobiosis lipoidica

Weak	There is a weak recommendation for treating necrobiosis lipoidica with fumarates. It is uncertain if the beneficial effects outweigh the safety aspects.

Remarks on clinical recommendation for necrobiosis lipoidica

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	- One study has demonstrated some effect of fumarates in patients with necrobiosis lipoidica. Very uncertain estimate. - Uncertainty about the safety of fumarates. - Costs may vary with the number of follow-up visits and dosage of fumarates.
Importance of the outcome that treatment prevents	-Complete remission of cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	- Good
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- Clinical score: ulceration, erythema, infiltration and pain. Histological score. Ultrasound assessment. Uncertain.
Risks associated with therapy	- Side effects of fumarates
Burdens of Therapy	- See risks. Daily oral administration of tablets. Frequent laboratory testing on blood and urine samples
Risk of target event	- Target event is necrobiosis lipoidica; so risk is 100%.
Costs	- Costs of fumarates are € 30,32 for 7 days 1dd 720 mg, not included are the costs for delivery, laboratory monitoring, and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Little varying values between patients
Other	- There are other treatment options available.

References

Kreuter A, Knierim C, Stücker M, Pawlak F, Rotterdam S, Altmeyer P, Gambichler T. Fumaric acid esters in necrobiosis lipoidica: results of a prospective noncontrolled study. Br J Dermatol. 2005 Oct;153(4):802-7.

Psoriatic arthritis

Introduction
Only one study, published in 1992, was found in the literature in which patients with psoriatic arthritis were treated with fumarates. This study was a RCT.
Efficacy was measured by several clinical parameters, including joint paint, Ritchie articular index, body surface affected with psoriasis, and infiltration and erythema of the skin. In addition, laboratory parameters for inflammation, including erythrocyte sedimentation rate (ESR) and leukocyte count, were used as outcome measures.

RCT
Methodological quality
The RCT of Peeters et al. employed an adequate randomization and an adequate concealment of allocation. Both participants and outcome assessors were blinded. An overview of the methodological quality can be seen in the risk of bias table (Table 14).

Demography
Two treatment arms were compared in the study by Peeters et al. One arm was treated with Fumaderm, while the other treatment arm received matching placebo tablets. Duration of treatment was 16 weeks. The dosage of fumarates was increased according to a standardized incremental dosage regimen up to Fumaderm 215 mg six times a day depending on individual tolerability. There was no follow-up.
In total, 27 subjects (21 male, 6 female) were enrolled, with a mean age of 40 years. Only subjects with 2 or more inflamed joints and a Ritchie score exceeding 4 were considered for enrollment.

Efficacy
Peeters et al. found a significant decrease of joint pain and of Ritchie articular index after 16 weeks of treatment with dumarates. In addition, erythema of skin improved significantly. Affected body surface and infiltration improved, although not statistically significant. The ESR decreased significantly during fumarates treatment as well. Time to response was not mentioned.

Conclusion on strength of evidence for efficacy of fumarates in psoriatic arthritis

Moderate	The only available study was of high quality with small number of patients.

Magnitude of treatment effect

Very uncertain estimate for a moderate effect

Clinical recommendation for psoriatic arthritis

Weak	There is a weak recommendation for treating psoriatic arthritis with fumarates if conventional treatment options are contra-indicated or have failed. It is uncertain if the beneficial effects outweigh the safety aspects.

Remarks on clinical recommendation for Psoriatic arthritis

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	- One study has demonstrated effect of fumarates in psoriatic arthritis patients. Certain estimate. - Uncertainty about the safety of fumarates. - Costs may vary with the number of follow-up visits and dosage of fumarates.

Importance of the outcome that treatment prevents	- Complete remission cutaneous lesions and reduction of joint pain and Ritchie articular index.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	- Good
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- Clinical score, Ritchie score, inflammatory parameters (erythrocyte sedimentation rate , leukocyte counts).
Risks associated with therapy	- Side effects of fumarates
Burdens of Therapy	- See risks. Daily oral administration of tablets. Frequent laboratory testing on blood and urine samples
Risk of target event	- Target event is psoriatic arthritis; so risk is 100%.
Costs	- Costs of fumarates are € 30,32 for 7 days 1dd 720 mg, not included are the costs for delivery, laboratory monitoring, and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Little varying values between patients
Other	- There are other treatment options available.

References

Peeters AJ, Dijkmans BA, van der Schroeff JG. Fumaric acid therapy for psoriatic arthritis. A randomized, double-blind, placebo-controlled study. Br J Rheumatol. 1992 Jul;31(7):502-4.

Psoriasis pustulosa palmoplantaris

Introduction
One study in total, published in 2003, was found in the literature in which patients with psoriasis pustulosa palmoplantaris were treated with fumarates. This was a prospective case series.
Effectiveness was measured by a modified Psoriasis Area and Severity Index called the Psoriasis pustulosa palmoplantaris Area and Severity Index (PPPASI), which scores pustules and erosive lesions of both palmar and plantar sides. The scale ranges from 0 to 26, with higher scores indicating higher disease activity.

Case series
Demography
Thirteen patients (8 female, 5 male) suffering from isolated psoriasis pustulosa palmoplantaris were enrolled. The age of the subjects ranged from 25 to 78 years, with a mean age of 52.5 years. Patients who had received active antipsoriatic treatment within the previous 3 weeks were excluded. During this study no concomitant antipsoriatic therapy was allowed, except for bland topical treatment with petrolatum and with or without 5% salicylic acid.
The dosage of fumarates employed was up to Fumaderm 215 mg six times a day, and was individually adjusted. The study was designed for a treatment duration of 24 weeks. Eight patients completed the entire study duration, while the other 5 patients discontinued treatment after 8 to 12 weeks.

Effectiveness
After 24 weeks of treatment with fumarates, there was a mean reduction of PPPASI score of 49% for palmar lesions, and a mean reduction of 44% for plantar lesions, which corresponds with a total improvement of 75%. One patient had no change in PPPASI, and 1 patient had an increase in PPASI by more than 70%. Time to response was not reported.

Conclusion on strength of evidence for efficacy of fumarates in psoriasis pustulosa palmoplantaris

Very Low	The only available study was of very low quality with small number of patients and uncertainty about directiveness.

Magnitude of treatment effect

Very uncertain estimate for a moderate effect

Clinical recommendation for psoriasis pustulosa palmoplantaris

Weak	There is a weak recommendation for treating psoriasis pustulosa palmoplantaris with fumarates. It is uncertain if the beneficial effects outweigh the safety aspects.

Remarks on clinical recommendation for Psoriasis pustulosa palmoplantaris

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	- One study has demonstrated some effect of fumarates in psoriasis pustulosa palmoplantaris patients. Certain estimate. -Uncertainty about the safety of fumarates. -Costs may vary with the number of follow-up visits and dosage of fumarates.
Importance of the outcome that treatment prevents	-Complete remission cutaneous lesions.
Magnitude of treatment effect*	-Moderate

* the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- Psoriasis pustulosa palmoplantaris Area and Severity Index
Risks associated with therapy	- Side effects of fumarates
Burdens of Therapy	- See risks. Daily oral administration of tablets. Frequent laboratory testing on blood and urine samples
Risk of target event	- Target event is Psoriasis pustulosa palmoplantaris; so risk is 100%.
Costs	- Costs of fumarates are € 30,32 for 7 days 1dd 720 mg, not included are the costs for delivery, laboratory monitoring, and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Little varying values between patients
Other	-There are other treatment options available.

References

Ständer H, Stadelmann A, Luger T, Traupe H. Efficacy of fumaric acid ester monotherapy in psoriasis pustulosa palmoplantaris. Br J Dermatol. 2003 Jul;149(1):220-2.

Psoriasis

Introduction

A total of 23 studies, published between 1987 and 2010, were found in the literature, in which patients with psoriasis were treated with fumarates. Of these, 4 studies were RCT's, 2 were cohort studies, and 17 were case series.

Efficacy and effectiveness was measured by the decrease in the psoriasis area and severity index (PASI), in which the severity and extent of erythema, scaling, and induration are assessed. Several studies used an modified psoriasis severity score. Furthermore, efficacy was measured with the change in body surface affected (BSA) or with a global assessment, defined as complete clearance, good improvement, moderate improvement, and no improvement. In addition, effects on pruritus, nail psoriasis and joint complaints were used as outcomes for efficacy in several studies. Also, one study assessed changes in health-related quality of life.

RCT

Methodological quality

All four RCT's employed an adequate randomization, but in the studies of Gollnick et al. and Altmeyer et al. the concealment of allocation was not clearly described. All four studies were double-blinded. An overview of the methodological quality can be seen in the risk of bias table (Table 20).

Demography

Three of the RCTs were placebo-controlled trials. Only the study of Nieboer et al. had no placebo-arm, but compared the efficacy of two fumarates-formulations: one arm was treated with a fumarates-formulation similar to Fumaderm 215 mg, containing 120 mg DMF plus 95 mg MEF, while the other arm was treated with a fumarates-formulation containing only 120 mg DMF. The study of Gollnick et al. compared the efficacy of the combined treatment of Fumaderm 215 mg with a topical treatment (calcipotriol ointment 50 µg/g) with that of Fumaderm 215 mg with a placebo ointment. The study of Nugteren-Huying compared three treatment-groups: Fumaderm 215 mg (120 mg DMF and 95 mg MEF); tablets with 284 mg octylfumarate and 8 mg MEF; and placebo tablets.

Duration of treatment ranged from 3 to 4 months. Three RCT's applied a standardized incremental dosage regimen up to Fumaderm 215 mg six times a day. Only in the study of Nieboer et al. the dosage was increased up to Fumaderm 215 mg four times a day. None of the RCT's had a follow-up extension.

In total, 318 subjects were enrolled. All patients were aged 18 years or older. Patients had to have at least 10% body surface area affected to be considered for inclusion. The study of Gollnick et al. only mentioned to enroll severe psoriasis without giving further details.

Efficacy

Altmeyer et al. assessed in their multi-center randomized double-blind placebo-controlled trial the efficacy of treatment with Fumaderm in 100 patients with psoriasis. The mean PASI decreased from 21.57 at baseline to 10.77 at week 16. The time to response varied between 2 and 12 weeks.

In a single-center randomized controlled trial among 45 patients with psoriasis, Nieboer et al. compared the efficacy of a fumarate-formulation containing DMF and MEF with a formulation containing only DMF. The treatment response was similar in both groups, with approximately 50% of patients who had a 50% or greater improvement of their psoriasis following 4 months of treatment. No significant changes were observed between the two groups.

Nugteren-Huying et al. conducted a small randomized double-blind placebo-controlled trial to assess the efficacy of Fumaderm, a fumarate-formulation with octylfumarate, and placebo. In the Fumaderm group the mean percentage of affected body surface decreased from 21% to 6.7% following 16 weeks of treatment. In contrast, no significant improvement of affected body surface was seen in the octylfumarate group nor the placebo group.

In a multi-center randomized vehicle-controlled trial Gollnick et al. assessed the efficacy of the combined treatment with Fumaderm plus calcipotriol ointment and compared that with Fumaderm plus placebo ointment. Gollnick and al. reported a 76.1% PASI-reducation in the group treated for 13 weeks with Fumaderm plus calcipotriol versus a 51.9% reduction in PASI in the group treated with Fumaderm. In

addition, a faster response and a lower daily dosage of fumarates were observed in patients treated with fumarates plus calcipotriol.

Cohort

Methodological quality

Three cohort studies were included. All three studies are briefly described, and many methodological aspects are not clearly indicated.

Demography

In the cohort-study of Kolbach et al. two fumarate-formulations were compared: Fumaderm 215 mg (120 mg DMF and 95 mg MEF) four times a day versus a fumarates-formulation containing 60 mg DMF four times a day. The study of Friedrich et al. compared the side-effects of Fumaderm monotherapy with that of Fumaderm combined with pentoxifylline 400 mg twice a day. In total, 240 participants aged 18 years and older with psoriasis were included in these two studies. Friedrich et al. applied a standardized incremental dosage regimen up to Fumaderm 215 mg six times a day. Kolbach et al. used a modified dosage regiment with a maximum dosage of Fumaderm set at 215 mg four times a day, and in the other group 60 mg DMF four times a day. Treatment duration ranged from 1.8 to 24 months. There was no follow-up.

Nieboer et al. described the results of 3 different studies in 1 article. One study assessed the efficacy of DMF 240 mg per day compared to placebo, the second study assessed the efficacy of Natrium (Na)-MEF 240 mg per day compared to placebo, and the third study compared two dosages of Na-MEF: 240 mg versus 720 mg. Treatment duration was between 3 and 4 months, and there was no follow-up.

Effectiveness

In the study by Kolbach et al., the proportion of patients with a sufficient response, which was defined as more than 75% improvement, was 23 of 209 patients in the group with DMF versus 31 of 67 patients in the group with Fumaderm after 2 years of treatment. The proportion of patients who discontinued treatment was higher in the DMF group (108 of 129 patients) in comparison to the Fumaderm group (30 of 67 patients).

Friedrich et al. reported in their cohort study that there were no differences in antipsoriatic response between the group treated with Fumaderm only and the group treated with Fumaderm and pentoxifylline. No additional information about effectiveness was given in the article.

Nieboer et al. found that there were no differences in efficacy of na-MEF compared to placebo. By contrast, the effects of DMF were was statistically signifcantly better than placebo, as a total severity score decreased by 60% in the group treated with DMF while the score increased to 105% in the placebo-group ($p<0.01$). In a third sub-study, Nieboer et al. reported that the overall efficacy of Na-MEF 720 mg per day was not different to Na-MEF 240 mg per day

Case series

Demography

Seventeen studies with case series were included concerning a total of 1764 patients with psoriasis. Of these, 10 were prospective studies, and 7 were retrospective case series. The age of the subjects ranged from 14 to 81 years. A majority of the studies used Fumaderm with the standard dosage scheme up to a maximum daily dosage of 215 mg six times a day. However, in the study of Carboni et al. Fumaderm was used to a maximum of 215 mg three times a day. Kokelj et al. used a different fumarates-formulation (Psocaps), which contains 72 mg DMF and 42 mg MEF per tablet. Nieboer et al. described several studies in which different fumarates were assessed, including a DMF-formulation with a maximum daily dosage of 60 mg four times a day. In the study of Bayard et al. patients were advised to adhere to a specified diet in combination with Fumaderm.

Effectiveness

In a large prospective case series of Altmeyer et al among 83 patients with psoriasis a mean PASI reduction of 76% was observed after 12 months of treatment. In addition, Altmeyer et al. reported significant improvements of pruritus, nailpsoriasis, and arthralgia.

Carboni et al. reported in their prospective case series among 40 patients a mean PASI decrease from 26.5

to 5.3 after 6 months of treatment, with 25 of 40 patients who achieved a complete remission of their psoriasis.
In a small prospective case series among 10 patients, Höxtermann et al. reported a mean PASI decrease from 24.45 to 3.4 after 12 months.
Kokelj conducted a prospective case series of 41 patients with psoriasis who were treated with an Italian fumarate-formulation (Psocaps). In this study a mean PASI reduction was reported from 5.9 to 3.0 after 3 months of treatment.
In a prospective case series from the Netherlands, Litjens et al. reported a mean decrease of 22% in 12 patients with psoriasis following 6 months of treatment with Fumaderm.
Mrowietz et al. conducted a large multi-center prospective case series among 101 patients with psoriasis treated with Fumaderm. In this study the mean PASI decreased with 80% from 20.04 at baseline to 4.03 after 16 weeks of treatment. Also, pruritus, joint pain, and nailpsoriasis improved during treatment with Fumaderm.
Wain et al. reported in an English single-center prospective case among 80 psoriasis patients a PASI reduction from 13.6 to 9.3 after 6 months of treatment with Fumaderm. Seven of 80 patients reached a 75% or greater improvement of their PASI. In addition, dermatologic-specific health-related quality of life as measured by the Dermatology Life Quality Index (DLQI) significantly improved during Fumaderm treatment.
In a retrospective case series from Ireland, Brewer et al. assesed the effectiveness of Fumaderm in 31 patients. Ten out of 31 patients had an excellent improvement, 7 patients had a good improvement, while 4 patients had no response.
In a small retrospective case series among 12 psoriasis patients from a single center in England, Balasubramani et al. reported 2 patients with a well-controlled disease, 8 with clinical improvement, and 1 with a worsening of psoriasis following treatment with Fumaderm. One patient had to discontinue Fumaderm after 3 months because of side effects. In addition, in 7 patients there was a dose-sparing effect on their concomitant systemic therapy, while in 2 patients no other systemic was required anymore. In 2 patients, however, no change in dosage of the concomitant therapy occurred.
Sladden et al. retrospective analysed the effects of Fumaderm in 30 patients treated at their center in England. They reported a complete or virtual clearance in 15 patients, some improvement in 4 patients, and a exacerbation in 2 patients.
In another English retrospective study of Fika et al. among 11 patients with psoriasis who were treated with Fumaderm, 5 patients had a clearance of their psoriasis, 9 patients an improvement, and 2 patients who achieved no reponse.
Harries et al. retrospectively described the outcomes of treatment with Fumaderm among 58 patients with psoriasis at a single center from the United Kingdom. In this study, 10 patients achieved a clearance or virtually clearance, 22 patients with improvement, 16 patients with no improvement, and 9 patients with worsening of their psoriasis.
In a long-term retrospective case series from the Netherlands, Hoefnagel et al. reported that among a group of 38 patients who discontinued fumarates treatment, 4 patients had a clinical improvement, 9 had a lack of efficacy, and 23 had a exacerbation after an initial improvement.
Thio et al. reported in a large Dutch retrospective case series a very good improvement in 26 out of 83 patients, a good improvement in 15 patients, moderate improvement in 10 patients, and no improvement in 1 patient.
Reich et al. analysed the effects of Fumaderm in a large German multi-center cross-sectional study among patients treated with Fumaderm for at least 24 months. In this study 490 out of 566 patients had a complete or marked improvement after 36 months of treatment, while the mean PASI was reduced from 22.7 at baseline to 4.8 after 36 months of treatment with Fumaderm.
Nieboer et al. reported outcomes of fumarates in two prospective case series from 1989. In the first case series 36 patients treated with Fumaderm.
In the second case series by Nieboer et al., 56 treated with DMF
In a German publication from 1987 3 prospective case series were described by Bayard et al. In the first case series 2 of 13 patients treated with Fumaderm had a very good improvement, 3 patients had a good improvement, and 6 patients had a insufficiënt improvement. In a second sub-study with 5 patients, 1 patients had a very good improvement, and 4 had insufficiënt improvement. In the third sub-study

involving 12 patients treated with Fumaderm, 5 had a very good improvement, 1 had a good improvement, and 4 had no improvement.

Conclusion on strength of evidence for efficacy of fumarates in psoriasis

Good	The three available RCT's were of high quality. The cohort studies and case series supported the outcome of the RCT's.

Magnitude of treatment effect

Certain estimate for a good effect

Clinical recommendation for psoriasis

Strong	There is a strong recommendation for treating psoriasis with fumarates if conventional treatment options are contra-indicated or have failed.

Remarks on clinical recommendation for Psoriasis

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	- The RCT's have demonstrated good effect of fumarates in psoriasis patients. Certain estimate. -Uncertainty about the safety of fumarates. -Costs may vary with the number of follow-up visits and dosage of fumarates.
Importance of the outcome that treatment prevents	-Complete remission cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	Good
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- psoriasis area and severity index (PASI), body surface affected (BSA)
Risks associated with therapy	- side effects of fumarates
Burdens of Therapy	- see risks. Daily oral administration of tablets. Frequent laboratory testing on blood and urine samples
Risk of target event	- Target event is psoriasis; so risk is 100%.
Costs	- Costs of fumarates are € 30,32 for 7 days 1dd 720 mg, not included are the costs for delivery, laboratory monitoring, and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Little varying values between patients
Other	-There are other treatment options available.

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III. TABLES

Alopecia areata

Table 1. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of fumarates per day
Alopecia areata Case series							
Venten, 2006	Prospective case series FD	6	-	AA	10 (5/5)	32.1 (17-44)	215 mg 3 times a day: n=2, 215 mg 5 times a day: n=1, 215 mg 6 times a day: n=7.

Abbreviations: AA = Alopecia areata; FD = Fumaderm.

Table 2. Results

	Efficacy/ effectiveness	Time to response (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Alopecia areata Case series						
Venten, 2006	n=3 (30%) very good response; n=1 (10%) good response; n=2 (20%) moderate response; n=4 (40%) no benefit	-	-	-	Gastrointestinal complaints (2), lymphocytopenia*.	-

* = number of patients was not reported.

Cheilitis granulomatosa

Table 3. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of fumarates per day
Cheilitis granulomatosa Case series							
Jansen, 2007	Case series (pros-pective) FD	Mean: 5.8 (range: 5-6)	Mean 5.6, range: 4-8	Cg	5 (3/2)	35.2 (25-56)	Up to 215 mg 3 times a day

Abbreviations: Cg = cheilitis granulomatosa; FD = Fumaderm.

Table 4. Results

	Efficacy/ effectiveness	Time to response (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Cheilitis granulomatosa Case series						
Jansen, 2007	n=2 (40%) complete clearance of lip swelling; n=3 (60%) reduction of lip swelling: Lingua plicata remained unchanged in 3 of 3 patients.	1	No relapse within a mean follow-up period of 5.6 months (range 4–8)	-	Flushing (3), gastrointestinal complaints (3), lymphopenia (1), eosiniphilia (1).	-

Cutaneous sarcoidosis

Table 5. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of fumarates per day
Cutaneous sarcoidosis Case series							
Breuer, 2005	Case series	range < 1 to > 23	-	Sa	11 (1/10)	45.9 (34-67)	SDS up to 215 mg 6 times a day

Abbreviations: FD = Fumaderm. SDS = Standard dosage schedule: Dosage of 'Fumaderm initial' 105 mg is increased weekly from 1 up to 3 tablets daily. Hereafter, 'Fumaderm' 215 mg is started and increased weekly from 1 tablet up to a maximum of 6 tablets daily.

Table 6. Results

	Efficacy/ effectiveness	Time to response (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Cutaneous sarcoidosis Case series						
Breuer, 2005	n=3 (27%) cleared or marked improvement; n= 3 (27%) slight to moderate improvement; n=5 (45%) no improvement	-	Relapse 1 month after treatment stopped (n=1)	Oral glucocortico-steroids plus azathioprine (1)	Nausea (1), flushing (1), leucopenia (1), proteinuria (1).*	-

* Reported in the subgroup of patients who discontinued therapy

Disseminated granuloma annulare

Table 7. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of fumarates per day
Disseminated granuloma annulare Case series							
Weber, 2009	Case series FD	Mean: 5.9 (range 1–18)	-	Dga	8 (4/4)	64.2 (46-80)	SDS up to 215 mg 6 times a day
Eberlein-König, 2005	Case series (prospective) FD	Mean 4.3 (SD 2.4, range 1-8)	-	Dga	8 (0/8)	51.25 (19-72)	SDS up to 215 mg 6 times a day
Breuer, 2005	Case series FD	Range <1 to >14	-	Dga	13 (3/10)	51.5 (16-75)	SDS up to 215 mg 6 times a day

Abbreviations: Dga = Disseminated granuloma annulare; FD = Fumaderm; SDS = Standard dosage schedule: Dosage of 'Fumaderm initial' 105 mg is increased weekly from 1 up to 3 tablets daily. Hereafter, 'Fumaderm' 215 mg is started and increased weekly from 1 tablet up to a maximum of 6 tablets daily.

Table 8. Results

	Efficacy/ effectiveness	Time to response (months)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Disseminated granuloma annulare Case series						

Weber, 2009	n=1 (12.5%) complete clearance;
	n=4 (50%) marked improvement;
	n=1 (12.5%) slight to moderate improvement;
	n=2 (25%) no response
		Mean 3.7, range 1-6	-	-	Mild leucopenia (6), nausea (2), diarrhea (1), abdominal pain (1), eosinophilia (1)	-

Eberlein-König, 2005	N=3 (37.5%) remission; N=4 (50%) partial remission; N=1 (12.5%) unchanged Visual analogue scale: colour decreased from 80.1 ± 15.1 to 50 ± 31.8 ($p<0.01$). Reduction of elevation from 81.5 ± 23.2 to 37.75 ± 32.6 ($p<0.05$).	0.75	-	-	Diarrhea (2), dizziness (2), nausea (1), flush (1), stomach pain (1).	-
Breuer, 2005	N=2 (15%) cleared or marked improvement; N=6 (46%) slight to moderate improvement; N=5 (38%) no improvement	7.7 weeks**	Relapse 3 months after treatment stopped (n=1)	topical corticosteroids (n=4), topical tacrolimus (n=1)**	Stomach complaints (3), diarrhea (2), elevated liver enzymes (1), leucopenia (1), lymphocytopenia (1), proteinuria (1), eosinophilia (1).*	-

* Only the adverse events reported by the patients who discontinued treatment.
** In the whole study group (n=32), included patients with granuloma annulare (n=13), annular elastolytic giant cell granuloma (n=3), cutaneous sarcoidosis (n=8), necrobiosis lipoidica (n=4), granulomatous cheilitis (n=1).

Necrobiosis lipoidica

Table 9. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of fumarates per day
Necrobiosis Lipoidica Case series							
Kreuter, 2005	Case series (prospective) FD	Mean 7.7 (SD 2.9, range 6-15)	Mean 9.3 (SD 5.8, range 6-28)	NL	18 (2/16)	43 (19-82)	SDS up to 215 mg 6 times a day

Abbreviations: FD = Fumaderm; NL = Necrobiosis Lipoidica; SDS = Standard dosage schedule: Dosage of 'Fumaderm initial' 105 mg is increased weekly from 1 up to 3 tablets daily. Hereafter, 'Fumaderm' 215 mg is started and increased weekly from 1 tablet up to a maximum of 6 tablets daily.

Table 10. Results

	Efficacy/ effectiveness	Time to response (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Necrobiosis Lipoidica case series						
Kreuter, 2005	- Decrease in mean ± SD clinical score, from 7.4 ± 1.8 (range 5-11) at baseline to 2.5 ± 1.3 (range 0-4) after therapy (P<0.001; 95% CI 4.12–6.01). - Four out of four patients with ulcerating NL achieved healing of the ulcers - Increase of dermal density: 19.1 ± 8.1 vs. 27.1 ± 10.1 (P<0.019; 95% CI -14.4 to -1.57). - Reduction of histological score: from 5.7 ± 1.9 at baseline to 3.9 ± 1.8 after therapy (P = 0.011; 95% CI 0.48–3.05).	-	During follow-up of at least 6 months, clinical outcome remained stable in all patients.	Emollients	Moderate lymphocytopenia (8), mild nausea (6), gastrointestinal complaints (6), flushing (3).	-

Psoriatic arthritis

Table 11. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of fumarates per day
Psoriatic arthritis RCTs							
Peeters, 1992	FD*	3.7	-	Pa	13 (10/3)	42.0 (SD 12.7)	Modified SDS up to 215 mg 6 times a day
	Placebo				14 (11/3)	39.4 (SD 9.6)	NA

Abbreviations: FD = Fumaderm; Modified SDS = Modified standard dosage schedule: Fumaderm 215 mg is increased weekly from 1 tablet up to a maximum dose of 6 tablets daily; NA, not applicable; Pa = Psoriatic arthritis.

* plus diet (no nuts, spices, wines and distilled products of wine)

Table 12. Results

	Efficacy/ effectiveness	Time to response (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Psoriatic arthritis RCTs						
Peeters, 1992	FD-group: Mean (SD) Ritchie articular index decreased from 13.0 (5.5) to 6.8 (4.5) (p=0.004) Mean (SD) patient's global assessment decreased from 2.2 (0.7) to 1.6 (1.5) (P=0.02) Mean (SD) of score of pain at rest decreased from 1.3 (1.0) to 0.5 (1.0) (P=0.04) Mean (SD) score of pain on active movement decreased from 2.4 (0.5) to 1.5 (0.9) (P=0.009) Mean (SD) body surface area affected with psoriasis decreased from 4.6 (5.2) to 1.5 (1.5) (not significant). Mean (SD) infiltration of the skin decreased from 1.4 (1.2) to 0.5 (0.7) (not significant) Mean (SD) score of erythema of skin improved from 1.6 (1.4) to 0.5 (0.6) (P=0.05). Only changes in body surface affected, infiltration of the skin, and erythema of the skin were statistically significant different between FD-group versus placebo-group, respectively P=0.006, P=0.005, and P < 0.001).	-	-	Indometacin (3), diclofenac (2), ibuprofen (2), 5% acidum salicylicum in vaseline	Diarrhea (9), flatulence (6), flushing (6), eosinophilia (6), bloated feeling (6), lymphopenia (5), nausea (5), headache (2)	-
	Placebo-group: Mean (SD) Ritchie articular index decreased from 12.3 (5.7) to 11.1 (7.8) (not significant) Mean (SD) patient's global assessment decreased from 2.1 (0.9) to 1.9 (1.1) (not significant) Mean (SD) of score of pain at rest decreased from 1.4 (0.7) to 1.1 (1.0) (not significant) Mean (SD) score of pain on active movement decreased from 2.3 (0.6) to 1.7 (0.9) (not significant) Mean (SD) body surface area affected with psoriasis changed from 3.3 (2.4) to 4.3 (4.8) (not significant). Mean (SD) infiltration of the skin changed from 2.2 (1.2) to 2.2 (1.2) (not significant) Mean (SD) score of erythema of skin changed from 1.9 (1.1) to 2.3 (1.2) (p=0.05).				Flushing (6), headache (6), diarrhea (4), bloated feeling (3), nausea (2), flatulence (1),	-

Table 13. Adverse events in RCT's en cohorts

	Peeters et al*		
Adverse events	**FD**	**Placebo**	**RR**
Infections	-	-	
Gastrointestinal symptoms	20	10	
Musculoskeletal symptoms	-	-	
Neurological symptoms	2	6	
Vascular symptoms	-	-	
Dermatological symptoms	-	-	
Drug hypersensitivity	-	-	
General side effects	6	6	
Malignancies	-	-	
Abnormalities in laboratory markers	11	-	
Serious adverse events	-	-	

Table 14. Risk of bias of included RCT

	Adequate randomisation?	**Adequate concealment of allocation?**	**Adequate blinding?**	**Incomplete data reported?**	**Free of selected reporting?**	**Free of other bias?**
Peeters, 1992	YES	YES	Participants YES Researchers YES Outcome assessment YES	NO	YES	YES

Psoriasis pustulosa palmoplantaris

Table 15. Characteristics of included articles

	Study design/ groups	**Treatment (months)**	**FU (months)**	**Disease of subjects**	***N* subjects (male/ female)**	**Mean age of subjects in years (range)**	**Dose of fumarates per day**
Psoriasis pustulosa palmoplantaris Case series							
Ständer, 2003	Case series (prospective) FD	Mean 5.5 (range 1.9-5.6)	-	Ppp	13 (5/8)	52.5 (25-78)	Modified SDS up to 215 mg 6 times a day

Abbreviations: FD = Fumaderm; Modified SDS = Modified standard dosage schedule: Fumaderm is increased weekly from 1 tablet up to a maximum dose of 6 tablets daily; Ppp = Psoriasis pustulosa palmoplantaris.

Table 16. Results

	Efficacy/ effectiveness	**Time to response (weeks)**	**Duration of remission (months)**	**Conco med (*n* of subjects)**	**AE's (*n* of events)**	**SAE's (*n* of events)**
Psoriasis pustulosa palmoplantaris Case series						
Ständer, 2003	After 8 weeks of treatment: n=2 (15%) PPPASI decrease of more than 70%; n=3 (23%) PPPASI decrease between 30-70%; n=6 (46%) PPASI decrease or increase 0-30% n = 1 (8%) PPASI increase 30-	-	-	Bland topical treatments	Gastrointestinal complaints (9), flushing (6), lymphopenia (3), increased liver enzymes (3), increase	-

	70% n=1 (8%) PPASI increase more than 70% After 8 weeks of treatment mean PPPASI decreased for palmer lesions from 12.5 to 9.4 (P=0.04), and for planter lesions from 14.1 to 11.1 (P=0.11). After 24 weeks of treatment mean PPPASI decreased for palmer lesions from 14.3 to 7.3 (P=0.004), and for plantar lesions from 13.0 to 7.2 (P=0.03). At week 24 an improvement of 75%, with a mean improvement of 49% and 44% for palmer and plantar lesions, respectively.				lipase values (1)	

Abbreviations: PPPASI = Psoriasis pustulosa palmoplantaris Area and Severity Index.

Psoriasis

Table 17. Characteristics of included articles

	Study design/ groups	**Treatment (months)**	**FU (months)**	**Disease of subjects**	***N* subjects (male/ female)**	**Mean age of subjects in years (range)**	**Dose of fumarates per day**
Psoriasis RCT's							
Gollnick, 2002	FD + placebo ointment	3	-	Ps	66 (50/16)	43.6	SDS up to 215 mg six times a day
	FD + calcipot	3			68 (44/24)	43.4	SDS up to 215 mg six times a day
Altmeyer, 1994	FD	3.7	-	Ps	50	41.1 (21-69)	SDS up to 215 mg six times a day
	Placebo	3.7			50	39.0 (19-67)	NA
Nieboer, 1990	FD	4	-	Ps	23	Range 18-70	Up to 215 mg four times a day
	DMF[#]	4			22		Up to 120 mg four times a day
Nugteren-Huying, 1990	FD	3.7	-	Ps	13 (8/5)	44.3 (20-67)	Modified SDS up to 215 mg six times a day
	OF[§]				13 (11/2)	43.7 (27-58)	Up to 292 mg six times a day
	Placebo				13 (9/4)	44.8 (24-73)	NA
Psoriasis Cohort studies							
Friedrich, 2001	FD	1.8	-	Ps	21	52.9	SDS up to 215 mg six times a day
	FD + pentox[*]	1.8			23		SDS up to 215 mg six times a day
Kolbach, 1992	DMF[¶]	Range 3-24	-	Ps	129	≥ 18	Up to 60 mg four times a day
	FD				67		Up to 215 mg four times a day
Nieboer, 1989	MEF-Na	4	-	Ps	19	≥ 18	Up to 60 mg four times a day
	Placebo	4	-		19		NA
Nieboer, 1989	DMF	4	-	Ps	22	≥ 18	Up to 60 mg four

							times a day
	Placebo	4	-		20		NA
Nieboer, 1989	MEF-Na	3	-	Ps	10	≥ 18	720 mg per day
	MEF-Na	3	-		10		240 mg per day
Psoriasis Case series							
Wain, 2010	Case series (prospective) FD	< 3 months (n=7), 3 months (n=70), 60 months (n=3)	-	Ps	80 (58/22)	44 (22-77)	SDS up to 215 mg six times a day
Reich, 2009	Case series FD	Mean duration of continuous treatment = 44.1 months, 46.6 with interruptions.	-	Ps	984 (572/411)	50.5 (15-105)	SDS up to 215 mg six times a day
Kokelj, 2009	Case series (prospective) Psocaps**	4	-	Ps	41 (23/18)	53 (27-81)	Up to 114 mg three times a day
Brewer, 2007	Case series FD	Mean 7.6 (range 0.5-18)	-	Ps	31 (21/10)	46.8 (27-78)	SDS up to 215 mg six times a day
Sladden, 2006	Case series FD	Not reported	-	Ps	30 (21/9)	52 (31-62)	SDS up to 215 mg six times a day
Fika, 2005	Case series FD	Not reported	-	Ps	11 (5/6)	43 (19-59)	SDS up to 215 mg six times a day
Harries, 2005	Case series FD	Not reported	-	Ps	58 (33/25)	47.2 (14-77)	SDS up to 215 mg six times a day
Balasubramaniam, 2004	Case series FD	Mean 10 (range 3-19)	-	Ps	12 (8/4)	49 (32-65)	SDS up to 215 mg six times a day
Carboni, 2004	Case series (prospective) FD	Mean 14.8 (range 1-24)	3	Ps	40 (25/15)	Median 46.2 (18-72)	Up to 215 mg three times a day
Hoefnagel, 2003	Case series FD	0-1 year (n=25), 1-5 years (n=22), 5-14 years (n=19)	-	Ps	66 (41/25)	52 (25-82)	SDS up to 215 mg six times a day
Litjens, 2003	Case series (prospective) FD	24	-	Ps	12 (5/7)	Median age 50 (men), 46 (females)	SDS up to 215 mg six times a day
Mrowietz, 1998	Case series (prospective) FD	3.7	-	Ps	101 (68/33)	43.4 (21-69)	SDS up to 215 mg six times a day
Höxtermann, 1998	Case series (prospective) FD	12	-	Ps	10 (7/3)	53 (44-66)	SDS up to 215 mg six times a day
Altmeyer, 1996	Case series (prospective) FD	12	-	Ps	83 (50/33)	46.1 (18-70)	SDS up to 215 mg six times a day
Thio, 1995	Case series FD	< 6 months; n=31, 6-24 months; n=33, 24-36 months; n=18, > 36 months; n=1	-	Ps	83 (29/23)*	48*	SDS up to 215 mg six times a day
Nieboer, 1989	Case series FD	9.7 (1-32)	-	Ps	36 (21/15)	Not reported	SDS up to 215 mg six times a day
Nieboer, 1989	Case series DMF	4-9	-	Ps	56	Not reported	60 mg one to four times a day
Bayard, 1987	Case series (prospective) FD	3	-	Ps	13	Not reported	SDS up to 215 mg six times a day
Bayard, 1987	Case series (prospective) FD + diet	4			5	Not reported	SDS up to 215 mg six times a day
Bayard, 1987	Case series (prospective) FD	12-14			12	Not reported	SDS up to 215 mg six times a day

Abbreviations: FD = Fumaderm; Calcipot = calcipotriol; MEF-Na = monoethylfumaric acid ester; NA= not applicable; SDS = Standard dosage schedule: Dosage of 'Fumaderm initial' 105 mg is increased weekly from 1 up to 3 tablets daily. Hereafter, 'Fumaderm' 215 mg is started and increased weekly from 1 tablet up to a maximum of 6 tablets daily.
[#]DMF = dimethyl Fumarates 120 mg
[¶]DMF = capsules filled with 60 mg of semi-enteric coated granulate of dimethyl fumaric acid ester.
[**]Psocaps, containing 42 mg MEF and 72 mg DMF.
[§]OF = 284 mg octyl hydrogen Fumarates, 5 mg magnesium monoethylFumarates, and 3 mg zinc monoethylFumarates.
[*]Pentox = pentoxifylline
* = of the 52 patients who were treated during an uninterrupted period of 6 or more months.

Table 18. Results

	Efficacy/ effectiveness	Time to response (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Psoriasis RCT's						
Gollnick et al. 2002	FD plus placebo ointment-group: decrease in PASI of 51.9% after 3 months	9	-	emollient cream	Gastro-intestinal side-effects (4), eosinophilia (2), renal colics (1), fatigue (1), loss of concentration (1), headache (1), increased sweating (1), itching (1), increase of liver enzymes (1)	-
	FD plus calcipotriol ointment-group: decrease in PASI of 76.1% after 3 months	3	-	emollient cream	Local irritation/allergic reaction (2), eosinophilia (2), gastro-intestinal side-effects, flush (1), itching (1), increase of liver enzymes (1)	Adnexitis (1)
Altmeyer, 1994	FD-group: Mean PASI decreases from 21.57 at baseline to 10.77 after 16 weeks of treatment. n=36 (72%) with complete, good, moderate or slight remission; n=9 (18%) no change; n=5 (10%) deterioration Arthralgia,but not nailpsoriasis, improved statistically significant compared to the placebo-group.	Between 2 and 12 weeks	-	Topical ointments and bath oils	Stomach-ache or cramps (35), diarrhea (27), flush (21), heat sensation (3), skin burning (2), pruritus (1), eosinophilia (1)	-
	Placebo-group: No change in mean PASI after 16 weeks of treatment. n= 9 (18%) with complete, good, moderate or slight remission; n= 41 (82%) no change or deterioration	-	-	Topical ointments and bath oils	Diarrhea (2), stomach-ache or cramps (2), skin burning (1)	-
Nieboer, 1990	FD-group: N=4 (17%) full clearance; N=12 (52%) improvement more than 50%; N=2 (9%) improvement between 25-50% ; N=1 (4%) with improvement less than 25%	-	-	-	Flushing (20), diarrhea (14), nausea/stomach (14), eosinophilia (3), albuminuria (2), leukopenia (2), lymphopenia (2), general malaise (1), headache (1), increase of ASAT/ALAT (1)	-
	DMF-group: N=4 (18%) full clearance; N=10 (45%) improvement more than 50%; N=3 (14%) improvement				Flushing (19), diarrhea (12), nausea/stomach (11), eosinophilia (8), lymphopenia (3),	

	between 25-50% ; N=5 (23%) with improvement less than 25%				leukopenia (3), general malaise (2), dizziness (1), headache (1), increase of alkaline phosphatase (1)	
Nugteren-Huying, 1990	FD-group: -Reduction of mean percentage of affected body surface from 21% to 6.7% after 16 weeks of treatment. n=6 (46%) with complete clearance; n=3 (23%) with improvement. Mean score for scaling decreased from 3.85 to 1.35; Mean score for infiltration decreased from 3.75 to 1.4; these changes were statistically different from the other two groups (P<0.01).	-	-	Topical treatment with 5% Salicylic acid in white petrolatum.	Flushing (12), diarrhea (12), increase of liver enzymes (8), bloating (7), fatigue (7), flatulence (6), nausea (6), headache (5), eosinophilia (5), dizziness (4), lymphopenia (4)	Renal insufficiency (1)
	OF-group: No improvement of mean percentage of body surface affected. No clearance of improvement. Mean score of scaling remained unchanged from 3.2 to 3.2 Mean score infiltration increased from 2.9 to 3.0				Diarrhea (12), flatulence (8), bloating (5), fatigue (5), nausea (4), flushing (4), elevation of liver enzymes (4)	-
	Placebo-group: No improvement of mean percentage of body surface affected n=1 (8%) improvement Mean score of scaling decreased from 2.7 to 2.2 Mean score of infiltration increased from 2.6 to 2.8				Flatulence (5), bloating (5), flushing (4), fatigue (3), headache (3), nausea (2), diarrhea (2), dizziness (1)	-
Psoriasis Cohorts						
Friedrich, 2001	FD monotherapy group: No differences in antipsoriatic response between the FD monotherapy group compared to the FD plus pentoxifylline group	-	-	Topical treatments allowed	76.2% with side-effects (not further specified); Mean (SEM) severity score for side-effects 3.48 (0.6); Proportion discontinuing due to side-effects 19%.	-
	FD plus pentoxifylline-group	-	-	Topical treatments allowed	52.2% with side-effects (not further specified); Mean (SEM) severity score for side-effects 1.91 (0.58); Proportion discontinuing due to side-effects 17.4%.	-
Kolbach, 1992	DMF-group: n=23 (18%) with a sufficient response (i.e. more than 75%	3	> 6	Topical treatment consisted of the	Gastrointestinal complaints, general malaise, flushing,	-

	improvement) after 24 months n=7 (5%) with an insufficient response (i.e. exacerbation, no improvement, or improvement less than 75%) after 24 months n=108 (84%) discontinued treatment within 24 months			application of a bland cream or ointment or a mild topical corticosteroid.	lymphopenia, leukocyopenia, mild deviation of liver functions (3), mild deviation of kidney function (1).	
	FD-group: n=31 (46%) with a sufficient response (i.e. more than 75% improvement) after 24 months n=8 (13%) with an insufficient response after 24 months n=30 (44%) discontinued treatment within 24 months					-

Nieboer, 1989	MEF-NA-group:
	n=1 (5%) more than 50% improvement;
	n=6 (32%) 25 to 50% improvement;
	n=9 (47%) 0 to 25% improvement
	n=3 (16%) deteriorated;
	
	No differences compared to placebo-group: only itching score was lower compared to placebo-group
		-	-	-	Flushing (16), gastrointestinal complaints (1), headache (1), dizziness (1)	

	Placebo-group:
	n=2 (11%) more than 50% improvement;
	n=5 (26%) 25 to 50% improvement;
	n=8 (42%) 0 to 25% improvement
	n=4 (21%) deteriorated;
		-	-	-		

Nieboer, 1989	DMF-group:
	n=6 (27%) more than 50% improvement;
	n=6 (27%) 25 to 50% improvement;
	n=4 (18%) 0 to 25% improvement
	
	Significant decrease of total score of 60% in DMF-group compared to a rise of 105% in placebo-group ($p<0.01$)
	
	Nail-improvement in 2 of 9 patients
	
	Improvement of arthritis in 2 of 3 patients
		6			Gastrointestinal complaints (16), lymphocytopenia (15), generalized malaise (6), flushing (6), proteinuria (2), leukocytopenia (2), increase of alkaline phosphatase (1)	

	Placebo-group:
	n=0 (0%) more than 50% improvement;
	n=1 (5%) 25 to 50% improvement;
	n=12 (60%) 0 to 25% improvement
	n=5 (25%) deteriorated					

Nieboer, 1989	720 mg MEF-NA-group:
	n=3 (30%) more than 50% improvement;
	n=4 (40%) 25 to 50% improvement;
	n=3 (30%) 0 to 25% improvement;
		-	-	-	Flushing (10), proteinuria (3), creatinine (2), BUN (2), increase of transaminase (2), increase of prothrombin time (2), increase of glucose time (2), increase of alkaline phosphatase (2), gastrointestinal complaints (1), headache (1), dizziness (1),	

	240 mg MEF-NA-group:
	n=3 (30%) more than 50% improvement;
	n=1 (10%) 25 to 50% improvement;
	n=6 (60%) 0 to 25% improvement:
		-	-	-		

Psoriasis Case series						

Wain et al. 2010	Mean (SD) PASI decreased with 19% from 13.9 (9.0) at baseline to 11.3 (9.2) after 3 months of treatment (P<0.0001).
	
	n=16 (20%) PASI-50;
	n=6 (8%) PASI-75;
	n=3 (4%) PASI-90;
	
	Mean (SD) DLQI decreased from 11.2 (7.3) to 8.5 (7.4) after 3 months of treatment (P<0.0001)
	
	Mean (SD) PASI decreased from 13.6 (9.5) to 9.3 (8.0) after 6 months of treatment.
	
	n=14 (31%) PASI-50;
	n=6 (13) PASI-75;
	n=3 (7) PASI-90;
	
	Mean (SD) DLQI decreased from 11.9 (7.1) to 6.0 (6.5) after 6 months of treatment.
		-	-	Acitretin (6), ciclosporin (29), methotrexate (11), mycophenolate mofetil (4), hydroxyurea (3), combinations of different treatments (6). Topical treatments allowed.	Diarrhea (29), lymphopenia (26), flushing (23), abdominal pain (20), eosinophilia (17), new-onset hypertension (6), increase in ALAT (1), increase in G-GT (1), nausea, malaise.	-

Reich, 2009	N=701 (78%) markedly improved/clear after 24 months of treatment N=490 (87%) markedly improved/clear after 36 months of treatment Reduction of mean PASI from 22.7 at baseline to 4.8 after 36 months of treatment**	-	-	-	Lymphopenia (369), leucopenia (108), increase of liver enzymes (117), elevation of creatinine (54)***	-
Kokelj et al. 2009	Mean PASI decreased 5.9 at baseline to 4.5 after 1 month of treatment, and to 3.0 after 4 months of treatment. n=19 (46%) improvement; n=10 (24%) no change n=6 (14%) worsening.	4	-	Emollients allowed	Flushing (9), gastrointestinal pain (2), folliculitis (1), nausea, abdominal pain	-

Brewer et al. 2007	n=10 (32%) excellent improvement;
	n=7 (23%) good improvement;
	n=4 (13%) failed.
		2.3 months (range 1-4 months)	-	Systemic therapies for first 2 months (6), hydroxyurea (2), acitretin (2), topical calcipotriol and	Flushing (21), diarrhea (19), lymphopenia (19), abdominal cramps (15), eosinophilia (10), nausea (5), leucopenia (5), increase in liver	carcinoma of the breast (1)

				emollients	enzymes (4), rash (1), fatigue (1)	
Sladden et al. 2006	n=15 (48%) clear or virtually clearance n=4 (13%) some improvement n=2 (6%) exacerbation psoriasis	-	-	-	Lymphocytopenia (13), gastro-intestinal complaints (8), flushing, microscopic hematuria (2).	Glomerulo-nephritis (1)
Fika et al. 2005	n=5 (45%) cleared n=4 (36%) improvement; n=2 (18%) no change	5.6 (range 3-8)	-	-	Abdominal upsets (9), lymphocytopenia (6), abdominal cramps (5), diarrhea (3), eosinophilia (3), flushing (2)	-

Harries et al. 2005	n=10 (17%) clear or virtually clearance;
	n=22 (38%) improvement;
	n=16 (28%) no improvement;
	n=9 (16%) worsening
		5.6 (range 2-20)	-	Concomitant therapy (21)	Abdominal pain (35), lymphocytopenia (33), diarrhoea (32), flushing (26), eosinophilia (18), nausea (12), malaise (9), elevation of liver enzymes (4), fatigue (2), hair loss (2), palpitations (2), flatulence (2)	-

Balasubramaniam et al. 2004	n=2 (17%) well-controlled;
	n=8 (67%) clinical improvement;
	n=1 (8%) worse;
	
	n=1 (8%) dose-sparing effect on concomitant systemic therapy;
	n=7 (58%) no change in dose concomitant therapy;
	n=2 (17%) no other systemic therapy required;
		-	-	Topical steroids (7), topical vitamin D3 analogues (6), ciclosporin (7), acetretin (4), methotrexate (2), hydroxyurea (3), no systemic therapies (2)	Flushing (10), flatulence (7), diarrhea (7), abdominal cramps (2), headache (2), increase in creatinine (2).	small well-differentiated squamous cell carcinoma (1)

Carboni et al. 2004	Mean PASI decreased from 26.5 to 5.3 after 6 months of treatment; n=25 (63%) complete remission; n=11 (28%) partial remission	Partial response at first month (n=24)	Within 1-3 months recurrences for 16 patients who discontinued treatment after 6 months	-	Flushing (11), abdominal cramps (8), itching (6), diarrhea (4)	-

Hoefnagel et al. 2003	n=4 (11%) clinical improvement;
	n=9 (24%) lack of efficacy;
	n=23 (61%) exacerbation after initial improvement
	of 38 patients discontinuing treatment:
		-	-	-	Lymphocytopenia (50), flushing (36), diarrhea (28), moderate increase of liver enzymes (17), nausea (9), fatigue (9), eosinophilia (9), abdominal complaints (8), itching (3), fever (1), dizziness (1)	-

Litjens et al. 2003	The mean (SD) PASI decreased to 22% (9%) of the baseline PASI after 6 months of treatment ($P < 0.05$).	3 months	-	Emollients	Eosinophilia (8), gastrointestinal complaints or flushing (5), leukocytopenia (4),	-
Mrowietz et al.	Mean reduction of 80% in PASI	-	-	Ointments	Gastrointestinal	-

1998	from 20.04 at baseline to 4.03 after 16 weeks of treatment. n=2 (2%) lack of efficacy Pruritus score decreased from 2.04 at baseline to 0.27 after 16 weeks of treatment Joint pain score decreased from 1.91 at baseline to 1.05 after 16 weeks of treatment Nail involvement decreased from 1.97 at baseline to 1.22 after 16 weeks of treatment			containing salicylic acid (<2%) or urea (<10%)	complaints (5), flush (1), increasing pruritus (1)	
Höxtermann et al. 1998	Mean PASI decreased from 24.34 at baseline to 5.36 after 6 months of treatment, and to 3.4 after 12 months of treatment. Mean remission index is 86% after 6 months of treatment.	4	-	Topical ointments and bath oils allowed	-	-
Altmeyer, 1996	Mean PASI decreased from 26.039 at baseline with 29% at month 1, 70% at month 4, and with 76% at month 12 to 2.238. N=35 (42%) complete remission; n=24 (29%) good improvement; n=9 (11%) no change. Pruritus decreased significantly from n=53 (62%) of patients with itch to n=2 (4%) after 12 months of treatment (p<0.001). Nailpsoriasis improved significantly with n=46 patients (55%) at baseline to n=21 (42.0%) after 12 months of treatment (p<0.001). Arthralgia improved significantly with n=24 (29%) at baseline to n=13 (26%) after 12 months of treatment (p<0.0019).	-	-	Emollients allowed	Lymphocytopenia (66), eosinophilia (44), flushing (43), diarrhea (27), leukocytopenia (17), abdominal pain (12), tenesmus (9), nausea (6), fatigue (4), increase in weight (3), burning eyes (2), increasing sweating (2), decreased appetite (2), decrease in weight (1)	-

Thio, 1995	n=26 (31%) very good improvement;
	n=15 (18%) good improvement;
	n=10 (12%) moderate improvement;
	n=1 (1%) no improvement
		-	At least 6 months	Topical antipsoriatic treatment with corticosteroids and anthralin (29), UVB-phototherapy (1)	Lymphocytopenia (35), flushing (28), elevated liver enzymes (21), fatigue (10), increased serum cholesterol (9), diarrhea (8), hyperkalemia (8), abdominal cramps (7), eosinophilia (6), proteinuria (6), hyperglycemia (4), nausea (3), increase of creatinine (2), dizziness (1), headache (1), mental depression (1)*	Renal insufficiency (2)

Nieboer, 1989	N=16 (44%) improvement more than 90%; n=23 (64%) improvement more	4-8	-	-	Gastrointestinal complaints (1)	-

	than 50% Arthritis complaints disappeared in 7 (70%) out of 10 patients with psoriatic arthritis.					

Nieboer, 1989	n=12 (21%) moderate improvement;
	n=18 (32%) considerable improvement;
	n=2 (4%) serious relapse;
	
	Improvement of arthritis complaints in 7 out of 9 patients. Nail abnormalities (n=15) showed little or no improvement.
		-	-	MEF-Na therapy (13)	Gastrointestinal complaints (11)	-

Bayard et al. 1987	n=2 (15%) very good improvement;
	n=3 (23%) good improvement;
	n=6 (46%) unsatisfactory improvement;
		-	-	Keratolytica and emollients allowed	Flushing (6), abdominal complaints (4), eosinophilia (2), metallic taste (1), cold feeling (1)	-

Bayard et al. 1987	n=1 (20%) very good improvement;
	n=0 (0%) good improvement;
	n=4 (80%) unsatisfactory improvement
		-	-	Keratolytica and emollients allowed	-	-

Bayard et al. 1987	n=5 (42%) very good improvement;
	n=1 (8%) good improvement;
	n=4 (33%) unsatisfactory improvement
		-	-	Topical corticosteroids (11), UV-B phototherapy	abdominal complaints (3), eosinophilia (2), flushing (2), urine hyaline casts (1), urine granular casts (1), swollen legs (1), heat feeling (1), headache (1), nausea (1)	-

* = of the 52 patients who were treated during an uninterrupted period of 6 or more months.
** = In the subgroup of patients with available PASI scores.
***= after 24 months except for elevation of liver enzymes (after three months)

Table 19. Adverse events in RCT's en cohorts

	Gollnick et al			**Altmeyer et al**			**Nieboer et al**			**Nugteren-Huying et al**			**Friedrich et al**			**Kolbach et al**		
Adverse events	**FD Plac**	**FD calc**	**RR**	**FD**	**Plac**	**RR**	**DF**	**DMF**	**RR**	**FD**	**OF**	**Plac**	**FD**	**FD pent**	**RR**	**FD**	**DMF**	**RR**
Infections	-	-		-	-		-	-		-	-	-	-	-		-	-	
Gastrointestinal symptoms	5	*		62	4		28	23		31	29	14	*	*		*	*	
Musculoskeletal symptoms	-	-		-	-		-	-		-	-	-	-	-		-	-	
Neurological symptoms	1	-		-	-		1	2		9	-	4	-	-		-	-	
Vascular symptoms	-	-		-	-		-	-		-	-	-	-	-		-	-	
Dermatological symptoms	1	1		3	1		-	-		-	-	-	-	-		-	-	
Drug hypersensitivity	-	2		-	-		-	-		-	-	-	-	-		-	-	
General side effects	1	1		24	-		21	21		19	9	7	*	*		*	*	
Malignancies	-	-		-	-		-	-		-	-	-	-	-		-	-	
Abnormalities in laboratory markers	3	3		1	1		10	15		17	4	-	-	-		*	*	
Serious adverse events	-	1		-	-		-	-		1	-	-	-	-		-	-	

* No number of patients mentioned.

Table 20. Risk of bias of included RCT

	Adequate randomisation?	Adequate concealment of allocation?	Adequate blinding?	Incomplete data reported?	Free of selected reporting?	Free of other bias?
Gollnick, 2002	YES	UNCLEAR	Participants YES Researchers YES Outcome assessment YES	NO	YES	YES
Altmeyer, 1994	YES	UNCLEAR	Participants YES Researchers YES Outcome assessment YES	NO	YES	YES
Nieboer, 1990	YES	YES	Participants YES Researchers YES Outcome assessment YES	NO	YES	YES
Nugteren-Huying, 1990	YES	YES	Participants YES Researchers YES Outcome assessment YES	NO	YES	YES