

## German evidence-based guidelines for the treatment of Psoriasis vulgaris (short version)

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**Abstract** Psoriasis vulgaris is a common and chronic inflammatory skin disease which has the potential to significantly reduce the quality of life in severely affected patients. The incidence of psoriasis in Western industrialized countries ranges from 1.5 to 2%. Despite the large variety of treatment options available, patient surveys have revealed insufficient satisfaction with the efficacy of available treatments and a high rate of medication non-compliance. To optimize the treatment of psoriasis in Germany, the Deutsche Dermatologische Gesellschaft and the Berufsverband Deutscher Dermatologen (BVDD) have initiated a project to develop evidence-based guidelines for the management of psoriasis. The guidelines focus on induction therapy in cases of mild, moderate, and severe plaque-type psoriasis in adults. The short version of the guidelines reported here consist of a series of therapeutic recommendations that are based on a systematic literature search and subsequent discussion with experts in the field; they have been approved by a team of dermatology experts. In addition to the therapeutic recommendations provided in this short version, the full version of the guidelines includes information on contraindications, adverse events, drug interactions, practicality, and costs as well as detailed

information on how best to apply the treatments described (for full version, please see Nast et al., JDDG, Suppl 2:S1–S126, 2006; or <http://www.psoriasis-leitlinie.de>).

**Keywords** Evidence-based guidelines · Psoriasis vulgaris · Treatment

### Introduction

The Deutsche Dermatologische Gesellschaft (DDG) and the Berufsverband Deutscher Dermatologen (BVDD) have initiated a project to develop evidence-based guidelines for the treatment of plaque psoriasis. The full version of the Guidelines has been published in the Journal der Deutschen Dermatologischen Gesellschaft (JDDG 2006 Suppl 2) and is available at <http://www.psoriasis-leitlinie.de> [149]. This article summarizes the key points of the Guidelines.

### Background

Psoriasis vulgaris is a common and chronic inflammatory skin disease which has the potential to significantly reduce the quality of life in severely affected patients. The incidence of psoriasis in Western industrialized countries is 1.5–2% [2]. Studies on the impairment of life quality have shown that, depending on the severity of the disease, a significant burden may exist in the form of a disability or psychosocial stigmatization [3]. Patient surveys have shown that the mental and physical impairment associated with psoriasis is comparable to that of other significant chronic conditions, such as type 2 diabetes or chronic respiratory diseases [4].

Patient surveys have shown that only 25% of psoriasis patients are highly satisfied with the outcome of their treatment, another 50% indicate moderate satisfaction, and approximately 20% report low treatment satisfaction [5]. In

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An enhanced version of these guidelines has been published with Blackwell in 2006.

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addition, there is a high non-compliance rate in the intake of medication of up to 40% [1].

Experience has shown that treatment selection for patients with psoriasis vulgaris is more commonly based on traditional concepts than on evidence-based data on the efficacy of various therapeutic options. In addition, it appears that systemic therapies are occasionally not applied in situations where they are needed due to the increased effort involved in monitoring the patients for unwanted side effects and possible interactions with other drugs.

### Goal of the Guidelines

The overall objective of the Guidelines is to provide dermatologists in clinics and private practice with an accepted

and evidence-based decision-making tool for the selection and implementation of a suitable and efficacious treatment for patients with psoriasis vulgaris. The focus of the Guidelines is on the induction therapy of mild, moderate, and severe plaque-type psoriasis in adults.

1. Physicians' personal experiences and traditional therapeutic concepts should be supplemented and, if necessary, replaced by an evidence-based assessment of the efficacy of individual therapies in psoriasis vulgaris.
2. The guidelines provide in-depth explanations of the available systemic and topical treatments for psoriasis, including the different photo- and photochemical therapies, and provide detailed descriptions of the administration and safety aspects.

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3. By providing background information on the profile of the available drugs, including efficacy, safety, and aspects of practicality and costs, the Guidelines should facilitate the process of selecting an appropriate treatment for each individual patient. This should help increase compliance and optimize the benefit/risk ratio of psoriasis therapies.

## Methods

A detailed description of the methodology employed in developing the Guidelines can be found in the Method Report on the Guidelines (<http://www.psoriasis-leitlinie.de>).

### Basis of data

A systematic search of the literature was carried out in May 2005 with the objective of assessing the effectiveness of individual therapeutic options. This search yielded 6,224 publications of which 142 studies fulfilled the inclusion criteria for the Guidelines (see Box 1) and were therefore included in the assessment of the effectiveness of the relevant treatment. Various other aspects were evaluated on the basis of information presented in available literature, without a systematic analysis, and the years of personal experience of the experts.

**Box 1** Studies had to fulfill the following criteria to be considered for the Guidelines' recommendations

- prospective study
- interim results <16 weeks
- exclusively adults
- ≥75% chronic plaque psoriasis
- severity of the skin lesions is described
- clear description of co-medication
- plausible dosage
- clear definition of effective outcome measures

### Evidence assessment

The efficacy and effectiveness of each intervention was evaluated using evidence-based criteria.

The methodological quality of each individual study was assessed using the following grades of evidence (GE):

- A<sub>1</sub> Meta-analysis that includes at least one randomized study with grade A<sub>2</sub> evidence. In addition, the results of the different studies included in the meta-analysis must be consistent with one another.
- A<sub>2</sub> A high-quality (e.g. sample-size calculation, flow chart, intention-to-treat (ITT) analysis, sufficient size) randomized, double-blind comparative clinical study.
- B Randomized clinical study of lesser quality or other comparative study (non-randomized, cohort, or case-control study).

- C Non-comparative study.
- D Expert opinion.

Individual interventions (i.e., as monotherapy) were rated according to the following levels of evidence (LE):

1. Intervention is supported by studies with grade A<sub>1</sub> evidence or studies with grade A<sub>2</sub> evidence whose results are predominantly consistent with one another.
2. Intervention is supported by studies with grade A<sub>2</sub> evidence or studies with grade B evidence whose results are predominantly consistent with one another.
3. Intervention is supported by studies with grade B evidence or studies with grade C evidence whose results are predominantly consistent with one another.
4. Little or no systematic empirical evidence

### Passages requiring consensus

The Guidelines Group defined particularly relevant sections as passages requiring consensus and approved these in the framework of the consensus conferences. These sections are highlighted in grey boxes.

### Therapeutic recommendation

A distinct rating of the therapeutic options or a strict clinical algorithm cannot be defined for the treatment of psoriasis vulgaris. The criteria for selecting a particular therapy are complex. The decision for a specific treatment should be based on the profile of the available drugs and the characteristics of a given patient. The decision for or against a therapy remains a case-by-case decision. These Guidelines provide a reasonable form of assistance in deciding on a suitable therapy and are an instrument for optimizing the required therapeutic process.

The recommendations formulated in the text are supported graphically in selected key recommendations by the following indications of the **strength of the therapeutic recommendation**:

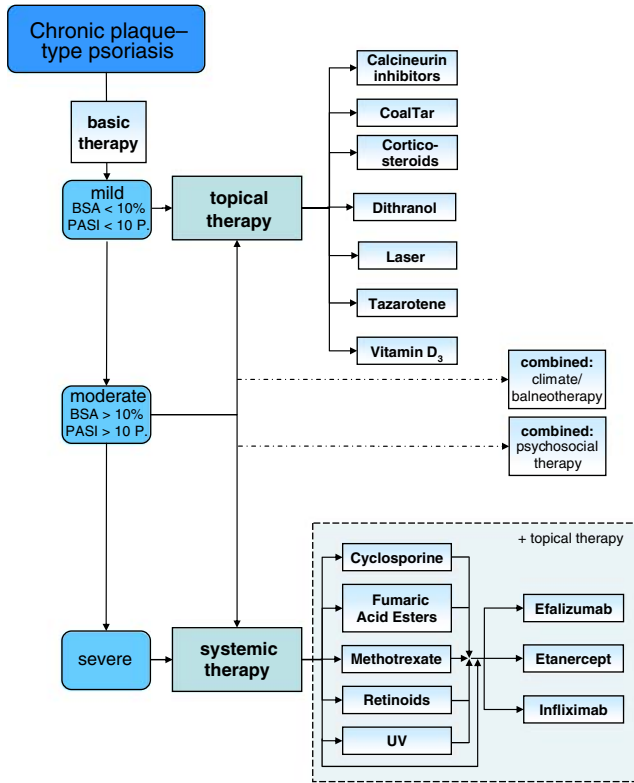
- ↑↑ Measure is highly recommended  
 ↑ Measure is recommended  
 → Neutral  
 ↓ Measure is not recommended  
 ↓↓ Measure is highly inadvisable

The strength of the recommendation reflects both a treatment's efficacy and the level of evidence supporting it as well as aspects of safety, practicality, and the cost/benefit ratio. A consensus on the strength of the recommendation was reached during the Consensus Conference.

**Results**

Therapeutic options are named and discussed in alphabetical order.

**Therapeutic strategies**



**Fig. 1** Overview of the therapeutic options evaluated for chronic plaque psoriasis (the therapeutic options are listed alphabetically and do not represent a ranking)

**Evaluation of topical and systemic therapies in tabular form**

These tables are intended to provide a rough orientation for evaluating the therapeutic options. Cumulative calculations of the individual aspects for the overall evaluation of the therapeutic options are not possible and cannot be drawn upon for the final analysis of a therapeutic option. The product assessment for each individual patient may deviate greatly. A direct comparison between systemic and topical therapies is not possible because of the different severity of the psoriasis lesions of patients treated with topical or systemic treatments. The evaluations reported here were made on the basis of data extracted from the literature and expert opinions.

For further details refer to the Methods Report at [www.psoriasis-leitlinie.de](http://www.psoriasis-leitlinie.de)

*Topical monotherapy*

Therapy	Efficacy	Safety/Tolerance Level of evidence	Safety/Tolerance in induction therapy	Safety/Tolerance in maintenance therapy	Practicality (patient)	Practicality (physician)	Cost/Benefit
Calcineurin Inhibitors	no assessment	4	++	not indicated	++	++	no assessment
Coal Tar	+/-	4	+	not indicated	-	+/-	-
Corticosteroids	++++ <sup>3)</sup>	1	+++	+	++	+++	+++
Dithranol	++	2	++	not indicated	+ <sup>1)</sup> - <sup>2)</sup>	+ <sup>1)</sup> - <sup>2)</sup>	+++
Tazarotene	++	2	++	++	++	++	++
Vitamin D <sub>3</sub> - Analogues	+++	1	+++	+++	++	+++	++

Global consideration: poor ← → good  
 -    +/-    +    ++    +++    ++++

- 1) inpatient
- 2) outpatient
- 3) potent (e.g. betamethason) or very potent corticosteroid (e.g. clobetasol), also valid for fix-combinations (vitamin D plus potent corticosteroids)

*Phototherapy and systemic monotherapy*

Therapy	Efficacy	Safety/Tolerance Level of evidence	Safety/Tolerance in induction therapy	Safety/Tolerance in maintenance therapy	Practicality (patient)	Practicality (physician)	Cost/Benefit	
Phototherapy	UVB	+++	2	+++	not indicated	+/-	+	++
	PUVA	+++ to ++++	2	+ <sup>1)</sup> ++ <sup>2)</sup>	not indicated	-	+/-	++
Acitretin <sup>3)</sup>	+	3	+	+	+	++	+/-	
Biologics	Efalizumab	+	1	++	++	+++	+	+
	Etanercept	+ <sup>4)</sup> ++ <sup>5)</sup>	1	++	++	+++	+	+
	Infliximab	+++ to ++++	1	+	++	+++	+/-	+
Cyclosporine	++ to +++	1	+	+	+++	++	++	
Fumaric Acid Esters	++	2	+	+++	++	+++	+++	
Methotrexate	++	3	+	+	++	++	+++	

Global consideration: poor ← → good  
 -    +/-    +    ++    +++    ++++

- 1) systemic PUVA
- 2) Bath- / Cream- PUVA
- 3) for women in childbearing age the therapy with retinoids is generally not recommended
- 4) for 2x25mg
- 5) for 2x50mg

(a) *Efficacy* The evaluation of the efficacy column reflects the percentage of patients who achieved a reduction in the baseline Psoriasis Area and Severity Index (PASI) of  $\geq 75\%$ .

Scale	Systemic therapy	Topical therapy
++++	Approx. 90%	Approx. 60%
+++	Approx. 70%	Approx. 45%
++	Approx. 50%	Approx. 30%
+	Approx. 30%	Approx. 15%
+/-	Approx. 10%	Approx. 5%
-	Not defined	Not defined

The evidence level applies only to the estimate of efficacy.

(b) *Safety/tolerance in induction therapy or maintenance therapy* This refers to the risk of occurrence of severe adverse drug reactions or the probability of adverse drug reactions that would result in the discontinuation of therapy.

(c) *Practicality (Patient)* This evaluation analyzes the effort involved in handling and administering the treatment regimen by the patient.

(d) *Practicality (Physician)* This aspect considers the amount of work (documentation, explanation, monitoring), personnel and equipment needs, time for physician/patient interaction, remuneration of therapeutic measures, invoicing difficulties/risk of recourse claims from the health insurance companies.

(e) *Cost/benefit* Consideration of the costs of an induction therapy or a maintenance therapy.

The evaluations of safety/tolerance in induction therapy or maintenance therapy as well as practicality for the physician or patient and the cost/benefit were performed using a scale ranging from poor (–) to good (++++). The gradation between these two extremes was made based on expert opinion and unsystematic literature search. A level of evidence was not given for these evaluations since no systematic literature review was performed.

## Evaluation of topical therapies

### Calcineurin inhibitors

**Table 1** Tabular summary

Calcineurin inhibitors	
First approved in Germany	
Pimecrolimus (Elidel®)	2002 (Atopic dermatitis, not approved for psoriasis vulgaris)
Tacrolimus (Protopic®)	2002 (Atopic dermatitis, not approved for psoriasis vulgaris)
Recommended initial dosage	Pimecrolimus cream: 1× to 2× daily Tacrolimus: 1× to 2× daily (application on the face: Begin with 0.03% salve; increase later dosage to 0.1% salve)
Recommended maintenance dosage	Individual therapeutic adjustment
Expected beginning of clinical effect	After approximately 2 weeks
Response rate	No data available
Important contraindications	Pregnancy and nursing (due to lack of experience) skin infections, immune suppression
Important adverse drug reactions (ADRs)	Burning sensation on skin, skin infections
Important drug interactions	None known
Other	<i>Cave: Do not combine with phototherapy! Photoprotection!</i>

### General assessment

Of the three studies with topical calcineurin inhibitors (pimecrolimus, tacrolimus) assessed, one study met the inclusion criteria of the Guidelines.<sup>[6]</sup> For that reason, the efficacy of psoriasis vulgaris treatment with topical calcineurin inhibitors can currently only be rated with a level of evidence of 4. Based on the studies to date, there is no evidence that monotherapy with calcineurin inhibitors is beneficial. Other studies have, however, demonstrated that topical calcineurin inhibitors can be beneficial in the treatment of psoriasis vulgaris in corticosteroid-sensitive areas such as the face, intertriginous areas, and the anogenital region.

Since topical calcineurin inhibitors are not approved treatment for psoriasis vulgaris, treatment may only be performed in off-label use.

The tolerance is generally good. Data on long-term safety are not available due to the relatively short-period of availability.

Broad usage as a first-line therapy does not appear to be justified by the existing data.

**Therapeutic recommendation**

Pimecrolimus and tacrolimus administered topically 1× to 2× per day can be considered to be a reasonable supplementary treatment of psoriasis vulgaris at specific locations of the body, such as the face, intertriginous areas and anogenital region (e.g. in interval therapy) or as a replacement for topical corticosteroids.



Watch for unwanted side effects such as burning and skin irritations.

Use at other body sites is not recommended.

*Corticosteroids***Table 2** Tabular summary

Corticosteroids	
First approved in Germany	1956 (Psoriasis vulgaris)
Recommended control parameters	None
Recommended initial dosage	One to two times daily
Recommended maintenance dosage	Gradual reduction following onset of effect
Expected beginning of clinical effect	After 1–2 weeks
Response rate	Betamethasone dipropionate, two times daily: marked improvement or clearance of the skin lesions in 46–56% patients after 4 weeks (LE 1)
Important contraindications	Skin infections, rosacea, perioral dermatitis
Important ADRs	Skin infections, perioral dermatitis, skin atrophy, hypertrichosis, striae
Important drug interactions	None
Other	–

**General assessment**

Of the 100 studies assessed for a monotherapy with corticosteroids, 20 fulfilled the Guidelines' inclusion criteria.<sup>[17-36]</sup>

With the application of potent corticosteroids (betamethasone dipropionate, 2× daily), 46–56% of the patients showed a clear improvement or a complete clearing of the skin lesions.

Therapy with very potent corticosteroids (clobetasol-17-propionate, 2× daily) demonstrated similar results in 68–89% of the patients in most studies.

Topical corticosteroids demonstrate a good to very good efficacy in the treatment of mild to moderate psoriasis vulgaris (LE 1).

The combination of topical corticosteroids with salicylic acid enhances the therapeutic effect.

Combination with other systemic or topical therapies also results in improved rates of remission. The most common combination is with topical vitamin D<sub>3</sub> derivatives.

There are no severe adverse drug reactions in the induction phase.

Care must be taken regarding the development of typical adverse corticosteroid effects such as skin atrophies or teleangiectases in cases of longer application and in particularly sensitive areas.

The practicality for physicians and patients is good.

**Therapeutic recommendation**

Therapy with topical corticosteroids is highly recommended for mild to moderate psoriasis vulgaris as a combination therapy with systemic therapies or other topical therapies.



The selection of the class of corticosteroids must be adjusted for the specific skin area to be treated.



## Coal tar

**Table 3** Tabular summary

Coal tar	
First approved in Germany	Listed active ingredient since 2000 (DAC on page 170), historical application, various tar-containing externals are licensed as drugs, application of tar as anti-psoriatic following publication by Goeckermann in 1925
Recommended control parameters	After long-term application/application on large areas: if needed clinical controls for potential development of skin carcinoma
Recommended initial dosage	5–20% salve preparations or gels for local therapy, 1× daily
Recommended maintenance dosage	No long-term application (max. 4 weeks, DAC 2000)
Expected beginning of clinical effect	After 4–8 weeks, efficacy improves in combination with UV application
Response rate	There is insufficient data available on the response rate as a monotherapy (LE 4)
Important contraindications	Pregnancy and nursing
Important ADRs	Color, odor, carcinogenic risk, phototoxicity—which is part of the desired effect
Important drug interactions	Not known with topical use
Other	DAC 2000 (on page 170), Hazardous Goods Directive Appendix 4 No. 13

**General assessment**

Of 19 studies assessed, four fulfilled the Guidelines' inclusion criteria.<sup>[37–40]</sup> Since only one monotherapy study was evaluated (with three patients), it is not possible to make a clear statement about the efficacy of monotherapy (LE 4).

Coal tar is used in clinical studies in combination with phototherapy.

In the combination therapy with UV light, a reduction of the PASI by about 75% was achieved in 45–80% of study participants after 15–20 applications. The additional effect of coal tar in combination therapy with UV compared to UV therapy alone has not been proven. The acceptance of coal tar is low due to its color and odor.

Magistral preparations may be less expensive than comparable manufactured products.

**Therapeutic recommendation**

The efficacy of coal tar treatment in psoriasis vulgaris has not been demonstrated, either as monotherapy or combination therapy. For this reason, coal tar is not recommended for this indication.



In view of the low-risk and more practical therapeutic alternatives, a monotherapy of psoriasis vulgaris with coal tar is obsolete.

Only after careful consideration of the therapeutic benefit and after low-risk therapeutic alternatives have failed should coal tar be used in combination with UVB in exceptional refractory cases of psoriasis vulgaris

## Dithranol

**Table 4** Tabular summary

Dithranol	
First approved in Germany	
Psoralon	1983 (Psoriasis vulgaris)
Psoradexan	1994 (Psoriasis vulgaris)
Micanol	1997 (Psoriasis vulgaris)
Recommended control parameters	Intensity of irritation
Recommended initial dosage	Begin with 0.5% preparation for long-term therapy or 1% for short-contact therapy, then increase if tolerated
Recommended maintenance dosage	Not recommended for maintenance therapy
Expected beginning of clinical effect	After 2–3 weeks
Response rate	Marked improvement or clearance of skin lesions in 30–50% of the patients (LE 2)
Important contraindications	Acute, erythrodermic forms of psoriasis vulgaris; pustular psoriasis
Important ADRs	Burning and reddening of the skin in >10%
Important drug interactions	–
Other	–

**General assessment**

Of 63 studies assessed for a monotherapy with dithranol, 11 fulfilled the Guidelines' inclusion criteria.<sup>[7-17]</sup>

The results of the studies assessed showed total remission (PASI reduction 100%) in 30–70% of the patients and partial remission (PASI reduction 75%) in 26–100% of patients after 5–8 weeks of treatment (LE 2).

The efficacy can be increased further if either calcipotriol creams or a UVB phototherapy is combined with dithranol.

Dithranol, one of the oldest topical therapeutics for psoriasis vulgaris, is still a treatment for mild to moderate psoriasis vulgaris as an out-patient monotherapy and as part of combination therapies for moderate psoriasis vulgaris in hospitalized and day clinic patients.

The therapy is very safe. Although skin irritations, burning, erythema and intermittent brown discolorations are observed, there are no systemic adverse drug reactions.

The practicality is clearly limited for outpatient use. The practicality for the physician, especially when treating inpatients, and the cost-benefit ratio are positive.

**Therapeutic recommendation**

Monotherapy for patients with mild and moderate psoriasis vulgaris is recommended for induction therapy during hospitalization



And conditionally recommended as an outpatient treatment.



Because it is more practical, short-contact therapy should be given preference. In hospitalized patients, classical dithranol therapy with 2× daily application without immediate rinsing can be easily performed.

The therapy should be performed for 4 and conditionally recommended as an outpatient treatment for 4–8 weeks. Maintenance or long-term therapy with dithranol is not practical and offers no advantages.

In the treatment of severe forms of psoriasis vulgaris, combination treatment with phototherapy or other topical preparations (calcipotriol) is recommended because of the improved response rate.



## Tazarotene

**Table 5** Tabular summary

Tazarotene	
First approved in Germany	1997 (psoriasis vulgaris)
Recommended control parameters	Check development of skin irritations
Recommended initial dosage	Begin with one treatment daily of tazarotene gel 0.05% in the evening for approximately 1–2 weeks
Recommended maintenance dosage	If necessary continue for 1–2 weeks with tazarotene gel 0.1%
Expected beginning of clinical effect	After 1–2 weeks
Response rate	After 12 weeks therapy with 0.1% tazarotene gel improved findings of at least 50% in approximately 50% of the patients (LE 2)
Important contraindications	Pregnancy, nursing
Important ADRs	Pruritus, burning sensation of skin, erythema, irritation
Important drug interactions	Avoid concomitant use of preparations with irritating and drying properties
Other	–

**General assessment**

Of the nine studies assessed, six fulfilled the Guidelines' inclusion criteria.<sup>[41–46]</sup>

After daily treatment with tazarotene 0.1%, approximately 50% of the patients showed at least a 50% improvement of the skin lesions after about 12 weeks of treatment (LE 2).

An optimization of the therapeutic success and a reduction of the frequent skin irritations can be attained with a combination of tazarotene and topical corticosteroids.

There are no severe adverse drug reactions. However, contact with healthy skin should be avoided to prevent skin irritation.

**Therapeutic recommendation**

The topical application of tazarotene is recommended for the treatment of mild to moderate psoriasis vulgaris.



An application of tazarotene in the evening in combination with a corticosteroid in the morning is recommended as a combination therapy to reduce irritation and increase efficacy.

Vitamin D<sub>3</sub> and analogues**Table 6** Tabular summary

Vitamin D <sub>3</sub> and analogues	
First approved in Germany	
Calcipotriol	1992 (Psoriasis vulgaris)
Tacalcitol	1994 (Psoriasis vulgaris)
Calcitriol	1999 (Psoriasis vulgaris)
Calcipotriol/ Betamethasone	2002 (Psoriasis vulgaris)
Recommended control parameters	Monitor for skin irritations
Recommended initial dosage	Calcipotriol: 1× to 2× daily to affected locations, up to a maximum of 30% of the body surface Tacalcitol: 1× daily to affected locations, up to a maximum of 20% of the body surface Calcitriol: 2× daily to affected locations, up to a maximum of 35% of the body surface
Recommended maintenance dosage	Calcipotriol: 1× to 2× daily, up to 100 g/week for up to 1 year Tacalcitol: 1× daily for 8 weeks, for up to 18 months, on a maximum of 15% of the body surface with up to 3.5 g daily Calcitriol: insufficient experience with the application for more than 6 weeks
Expected beginning of clinical effect	After 1–2 weeks
Response rate	Between 30 and 50% of the patients demonstrated a marked improvement or clearance of the lesions after 4–6 weeks (LE 1)
Important contraindications	Diseases with abnormal calcium metabolism, severe liver and renal diseases
Important ADRs	Skin irritation (reddening, itching, burning)
Important drug interactions	Drugs which elevate the calcium levels, (e.g. thiazide diuretics), no concomitant application of topical salicylic acid preparations (inactivation)
Other	Exposure to UV light results in inactivation of the vitamin D <sub>3</sub> -analogues

**General assessment**

Of the 39 studies considered, 11 fulfilled the Guidelines' inclusion criteria. <sup>[14, 22-25, 47-52]</sup>

The majority of available data is on calcipotriol. After vitamin D<sub>3</sub>-analogue treatment of mild to moderate psoriasis vulgaris, 30–50% of the patients showed a marked improvement or clearance of the skin lesions within a few weeks (LE 1).

The efficacy and tolerance can be further improved if the Vitamin D<sub>3</sub>-analogue is combined with topical corticosteroids during the initial therapy.

In the treatment of severely affected patients, topical therapy with vitamin D<sub>3</sub>-analogues demonstrated synergistic effects with a UV phototherapy and systemic cyclosporine therapy.

The topical vitamin D<sub>3</sub>-analogues are generally well-tolerated and practicable for the physician and the patient. Temporary skin irritations may limit the use, especially on the face or the intertriginous areas.

**Therapeutic recommendation**

Vitamin D<sub>3</sub>-analogues are the treatment of choice, especially for maintenance therapy in mild to moderate psoriasis vulgaris.



On the basis of the extensive study data and the superior efficacy, this recommendation is particularly true for calcipotriol. Because of its low irritating potential, the application of tacalcitol is particularly recommended for sensitive areas (e.g. face).

In the first weeks, use together with topical corticosteroids or as a fixed combination is superior to monotherapy with respect to efficacy and tolerance.



For moderate to severe psoriasis vulgaris, a combination of topical vitamin D<sub>3</sub>-analogues with UV phototherapy or a systemic therapy can be recommended.

**Phototherapy**

**Table 7** Tabular summary

Phototherapy	
First approved in Germany	Clinical experience, depending on the modality for >50 years
Recommended control parameters	Regular skin inspection (UV erythema)
Recommended initial dosage	Individual dose depends on skin type; options: <ul style="list-style-type: none"> <li>• UVB: 70% of minimum erythema dose (MED)</li> <li>• Oral PUVA (photochemotherapy): 75% of the minimum phototoxic dose (MPD)</li> <li>• Bath/cream PUVA: 20–30% of MPD</li> </ul>
Recommended maintenance dosage	Increase according to degree of UV erythema
Expected beginning of clinical effect	After 1–2 weeks
Response rate	In >75% of the patients PASI, 75 after 4–6 weeks (LE 2)
Important contraindications	Photo-dermatoses/photosensitive diseases, skin malignancies, immunosuppression Only PUVA: pregnancy and nursing
Important ADRs	Erythema, itching, blistering, malignancies Only oral PUVA: nausea
Important drug interactions	Drugs causing phototoxicity or photoallergy
Other	Combination with topical preparations acts synergistically, PUVA may not be combined with cyclosporine

**Instructions for application**Pre-treatment

- ◆ The attending physician has to perform a complete skin examination, paying special attention to melanocytic nevi (especially if dysplastic) and cutaneous malignancies.
- ◆ The patient has to be informed about unwanted side effects and possible long-term risks – especially the therapy-related increased risk of skin cancer. Additional UV exposure as a result of leisure-time activities should be considered. Written informed consent must be obtained.
- ◆ Before starting oral PUVA therapy, an ophthalmologic examination and the prescription of UV sunglasses is required.

During treatment

- ◆ The UV dosages applied must be documented in precise physical units ( $J/cm^2$  or  $mJ/cm^2$ ). Regular monitoring of UV erythema must be performed for the purpose of dosage increase.
- ◆ The medical records should document therapeutic response, unwanted side effects, and accompanying treatments.
- ◆ Eye protection with UV glasses is generally required.
- ◆ If the areas chronically exposed to light (face, neck, backs of hands) and the genital region are free of lesions, these should be protected from exposure.
- ◆ Adequate protection from the sun must accompany therapy.

Post-treatment

- ◆ Whenever a course of therapy is completed, the cumulative UV dosage and the number of treatments should be recorded and the patient has to be informed.
- ◆ Particularly in the case of patients with high cumulative UV dosage, a regular skin cancer examination should be performed for the patient's entire life.

**General assessment**

Of the 145 studies on monotherapy or combination therapy assessed, 25 studies on phototherapy, 32 studies on PUVA therapy, and five studies on therapeutic procedures with lasers fulfilled the Guidelines' inclusion criteria.<sup>[37–40, 53–100]</sup>

About three-quarters of all the patients treated with phototherapy attained at least a 75% PASI score reduction after 4–6 weeks, and clearance was frequently achieved (LE 2).

Phototherapy represents a safe and very effective modality for the treatment of moderate to severe forms of psoriasis vulgaris. The onset of the clinical effects is within 2 weeks.

Of the unwanted side effects, UV erythema from overexposure is by far the most common and is observed frequently. With repeated or long-term application, the consequences of high, cumulative UV dosages (i.e. premature aging of the skin) must be taken into consideration. In addition, carcinogenic risk is associated with oral PUVA and is probable for local PUVA and UVB.

The practicality of the therapy is limited as a result of the spatial, financial, and human aspects as well as by time resources on the part of the physician as well as the amount of time required by the patient.

From the perspective of the cost-bearing institution, phototherapy has a good cost-benefit ratio. However, the potentially significant costs and time required of the patient must be noted.

**Therapeutic recommendation**

Phototherapy is recommended as an induction therapy for moderate to severe psoriasis vulgaris, above all for widespread involvement.



The side effects of specific types of radiation must be weighed. A possible subsequent risk of skin cancer is better documented for PUVA than for UVB.

Due to its low practicality and the association of long-term unwanted side effects with the cumulative UV doses, phototherapy is not suitable for long-term treatment.



Combination with topical vitamin D<sub>3</sub>-analogues is recommended to improve the response rate.



A recommendation for the common combination with dithranol and corticosteroids can only be given on the basis of clinical experience, but not on the basis of scientific data.



The use of Excimer Lasers should be limited to the targeted treatment of individual psoriatic plaques.



## Evaluation of systemic therapies

### Efalizumab

**Table 8** Tabular summary

Efalizumab	
First approved in Germany	September 2004 (psoriasis vulgaris)
Recommended control parameters	Prior to therapy exclusion of significant infections, complete blood count, liver values
Recommended initial dosage	0.7 mg/kg body weight (BW) per week
Recommended maintenance dosage	1 mg/kg BW per week
Expected beginning of clinical effect	After 4–8 weeks
Response rate	PASI 75 for approximately 30% of the patients after 12 weeks (LE 1)
Important contraindications (limited selection)	Chronic or acute infections, pregnancy, malignant diseases, immune deficiencies, no vaccinations before or during treatment
Important ADRs (limited selection)	Flu-like injection reactions, leukocytosis and lymphocytosis, rebound, exacerbation and arthralgia, thrombocytopenia
Important drug interactions	Not known
Other	Stop therapy due to the risk of exacerbation and rebound if a PASI reduction of 50% is not achieved after 12 weeks

### Instructions for application

#### Pre-treatment

- ◆ Exclusion of severe systemic (acute and chronic) and local infections (e.g. abscesses)
- ◆ Reliable contraception and exclusion of pregnancy in women of childbearing age
- ◆ Patients should be made aware of the risks of and be monitored for severe infections
- ◆ Laboratory controls (see Table 3.5.1.1.2)

#### During treatment

- ◆ Exclusion of infections; the therapy should at least be temporarily discontinued when there is a suspicion of such.
- ◆ After 12 weeks of treatment, assessment of the therapeutic success: in case of good results (PASI > 50% improvement), treatment with efalizumab can be continued; otherwise, the treatment should be discontinued.
- ◆ In case of an exacerbation, another suitable psoriasis therapy should be introduced. In this case, other biologics should be considered.
- ◆ Laboratory controls (see Table 3.5.1.1.2)

#### Post-treatment

- ◆ Patients, who discontinue efalizumab should be subject to close follow-up.
- ◆ In cases of reoccurrence or exacerbation of the disease, the introduction of another suitable psoriasis treatment is recommended.
- ◆ Patients should be informed about the possibility of the occurrence of a rebound, which would make an immediate consultation necessary.

**Table 9** Laboratory controls during treatment with efalizumab

Period in months → Diagnostics ↓	Before	1	2	3	4	5	6	9
Complete blood count <sup>a</sup>	x	x	x	x	x	x	x	x
ALT, AST <sup>b</sup>	x			x				

<sup>a</sup> Hb (hemoglobin), HCT (hematocrit), erythrocytes, leukocytes, differential blood count, platelets

<sup>b</sup> ALT alanine aminotransferase, AST aspartate aminotransferase

**General assessment**

All six of the studies assessed in terms of the efficacy of therapy with efalizumab fulfilled the Guidelines' inclusion criteria.<sup>[101-106]</sup>

Approximately 30 and 40% of those patients with moderate to severe psoriasis vulgaris treated with efalizumab at a dose of 1 mg/kg BW per week attained a PASI reduction of > 75% (LE 1) within 12 weeks and 24 weeks, respectively.

As a result of the only once-per-week subcutaneous injection and the only rarely required medical controls, the therapy is highly practicable for both the patient and the attending physician.

Based on current knowledge, efalizumab possesses a favorable safety profile.

A follow-up of a larger patient population for a longer period of time is necessary for a definitive assessment of the efficacy and safety as a long-term treatment.

Compared to other biologics, experience with efalizumab is significantly lower due to the smaller patient populations which have been treated with efalizumab.

Disease exacerbation during therapy or a rebound after therapy has been observed.

**Therapeutic recommendation**

Efalizumab is recommended for induction therapy of moderate to severe psoriasis vulgaris especially if other therapeutic options have not demonstrated sufficient therapeutic effect, are not tolerated, or are contraindicated.



Therapy should not be continued if an improvement of at least 50% of the initial findings is not observed after the first 12 weeks of treatment.

*Etanercept***Table 10** Tabular summary

Etanercept	
First approved in Germany	2002 (Psoriasis arthritis )/2004 (psoriasis vulgaris)
Recommended control parameters	Prior to therapy exclusion of tuberculosis, complete blood count, liver and renal values, urinalysis
Recommended initial dosage	Twice 25 mg per week or 2× 50 mg/week
Recommended maintenance dosage	Twice 25 mg per week
Expected beginning of clinical effect	After 4–8 weeks, at the latest after 12 weeks
Response rate	PASI 75 in 34% (2 × 25 mg) or 49% (2 × 50 mg) of the patients at the end of the induction phase (12 weeks) (LE 1)
Important contraindications (limited selection)	Infections, pregnancy, nursing, heart failure NYHA III–IV
Important ADRs (limited selection)	Local reactions, infections
Important drug interactions (limited selection)	Anakinra (IL-1 receptor antagonist)
Other	–

**Instructions for application**Pre-treatment

- ◆ Exclusion of acute and chronic infections. An absolute exclusion of tuberculosis in accordance with the recommendations by the Paul Ehrlich Institute ([www.pei.de](http://www.pei.de))
- ◆ Reliable contraception and exclusion of pregnancy for women of child-bearing age
- ◆ Patients should be made aware of the risk of severe infections

During treatment

- ◆ At each visit, presence of infections should be excluded; the therapy should, at least temporarily, be discontinued in suspicious cases
- ◆ Monitoring for infections
- ◆ Etanercept therapy should be terminated or temporarily discontinued if there are signs of severe infection
- ◆ Discontinuation of therapy in case of onset of pregnancy
- ◆ Continued treatment with etanercept after 12 weeks if response is good, otherwise therapy should be discontinued

Post-treatment

- ◆ None

**Table 11** Laboratory controls during treatment with etanercept

Period in months → Diagnostics ↓	before	1	3	6	8
Diff. Blood count	x	x	x	x	x
ALT, AST	x	x	x	x	x
Pregnancy test (urine)	x				

### General assessment

Of the four studies assessed, three fulfill the Guidelines' inclusion criteria.<sup>[107-109]</sup>

During etanercept therapy, approximately 35% of the patients attained a PASI reduction of 75% after 12 weeks with two subcutaneous doses of 25 mg per week. With a therapy with 2× 50 mg subcutaneous per week for 12 weeks approximately 50% of the patients attained a PASI reduction of 75% (LE 1).

Clinical experience has shown that clinical efficacy can be maintained in a long-term therapy for up to 24 weeks.

The therapy is practicable for both the patient and the physician.

As a result of the large number of patients treated with etanercept for other indications, the risk of adverse drug reactions can be estimated very well.

### Therapeutic recommendation

Etanercept is recommended for induction therapy for patients with moderate to severe psoriasis vulgaris, especially if other therapeutic options have not demonstrated satisfactory therapeutic success, are not tolerated, or are contraindicated.



If concomitant psoriasis vulgaris and relevant psoriasis arthritis are present, treatment with TNF-alpha antagonists is particularly recommended.

## Infliximab

**Table 12** Tabular summary

Infliximab	
First approved in Germany	2004 (Psoriasis arthritis)/2005 (psoriasis vulgaris)
Recommended control parameters	Prior to therapy exclusion of tuberculosis, during therapy: leukocyte and platelet counts, liver value controls, signs of clinical infection
Recommended initial dosage	5 mg/kg BW at week 0, 2, 6
Recommended maintenance dosage	5 mg/kg BW in dosage intervals of 8 weeks
Expected beginning of clinical effect	After 1–2 weeks
Response rate	PASI 75 in ≥80% of the patients with moderate to severe psoriasis vulgaris (LE 1)
Important contraindications (limited selection)	Acute or chronic infections, tuberculosis, cardiac failure NYHA III–IV, pregnancy and nursing
Important ADRs (limited selection)	Infusion reactions, severe infections, progression of heart failure NYHA III–IV, very rare liver failure, autoimmune phenomena
Important drug interactions (limited selection)	Anakinra (IL-1 receptor antagonist)
Other	–

### Instructions for application

#### Pre-treatment

- ◆ Exclusion of acute and chronic infections, absolute exclusion of tuberculosis in accordance with the current recommendations of the Paul Ehrlich Institute ([www.pei.de](http://www.pei.de))
- ◆ Reliable contraception and exclusion of pregnancy in women of childbearing age
- ◆ Patients should be informed about the risk of severe infections.
- ◆ Hand out user information and special comment card to patients

#### During treatment

- ◆ Monitoring during infusion and 1–2 hours thereafter
- ◆ Monitoring for infections; the therapy should at least be temporarily discontinued when an infection is suspected

#### Post-treatment

- ◆ In women of childbearing age, contraception for up to 6 months after infliximab therapy



**Table 13** Laboratory controls during treatment with infliximab

Period in months→ Diagnostics↓	Before	1	2	3
Complete blood count <sup>a</sup>	x	Prior to start of therapy and before every infusion		
AST, ALT	x	Prior to start of therapy and before every infusion		
Pregnancy test (urine)	x			

<sup>a</sup>Hb, HCT, erythrocytes, leukocytes, differential blood count, platelets

### General assessment

Of the seven studies evaluated, four fulfill the Guidelines' inclusion criteria.<sup>[110-113]</sup>

Approximately 88% of the patients with moderate to severe psoriasis showed a PASI reduction of 75% after 10 weeks infliximab treatment with a dose of 5 mg/kg BW in the normal therapy intervals (LE 1).

Infliximab is currently one of the most effective drugs for the treatment of psoriasis vulgaris. On the basis of the data available from long-term studies, good efficacy is also expected in the long-term therapy of psoriasis vulgaris.

A number of safety aspects should be considered with infliximab. Amongst these are, above all, infusion reactions and the risk of severe infection. This requires a careful evaluation of the indication, education, as well as monitoring of the patient.

As a result of the large number of patients treated with infliximab for other indications, the risk of adverse drug reactions can be estimated very well.

### Therapeutic recommendation

Infliximab is recommended for the induction therapy of moderate to severe psoriasis vulgaris and severe, special forms of psoriasis which cannot be controlled by other therapeutic options or if, on the basis of the severity of the disease, a rapid resolution is required.

If concomitant psoriasis vulgaris and relevant psoriasis arthritis are present, treatment with TNF-alpha antagonists is particularly recommended.



## Cyclosporine

**Table 14** Tabular summary

Cyclosporine	
First approved in Germany	1983 (Transplantation medicine) 1993 (Psoriasis vulgaris)
Recommended control parameters	Interview/examination: <ul style="list-style-type: none"> <li>• Status of skin and mucous membranes</li> <li>• Signs of infection</li> <li>• Neurological, gastrointestinal symptoms</li> <li>• Blood pressure</li> </ul> Laboratory controls: see Table 14
Recommended initial dosage	2.5–3 (max. 5) mg/kg BW
Recommended maintenance dosage	Interval therapy (between 8 and 16 weeks) with dosage reduction at the end of the induction therapy (e.g., 0.5 mg/kg BW every 14 days) or Continuous long-term therapy with dosage reduction (e.g. by 50 mg every 4 weeks after week 12) and a dosage increase by 50 mg with relapse
Expected beginning of clinical effect	Maximum total duration of therapy: 2 years After approximately 4 weeks
Response rate	Dose-dependent: after 8–16 weeks with 3 mg/kg BW; PASI 90 in approximately 30–50% of patient and PASI 75 in approximately 50–70% of patients (LE 1)
Important contraindications (limited selection)	<b>Absolute:</b> Reduced renal function, insufficiently controlled arterial hypertension, uncontrolled infections, relevant malignancies (current or previous, in particular hematologic diseases and cutaneous malignancies with the exception of basal cell carcinoma) <b>Relative:</b> Relevant hepatic dysfunction, pregnancy and nursing, concomitant use of substance which interacts with cyclosporine, concomitant UV-therapy or prior PUVA-pre-therapy with cumulative dosage >1000 J/cm <sup>2</sup> , concomitant application of other immunosuppressives, retinoids or long-term prior-therapy with methotrexate (MTX)

**Table 14** continued

Cyclosporine	
Important ADRs (limited selection)	Renal failure, increase of blood pressure, liver failure, nausea, anorexia, vomiting, diarrhea, hypertrichosis, gingival hyperplasia, tremor, weariness, parasthesia, hyperlipidemia
Important drug interactions (limited selection)	<p>Increase of the cyclosporine level (CYP3A inhibition) through: Allopurinol, calcium antagonists, amiodarone, antibiotics (macrolides, clarithromycin, josamycin, ponsinomycin, pristinamycin, doxycycline, gentamicin, tobramycin, ticarcillin, quinolones), ketoconazole, oral contraceptives, methylprednisolone (high dosages), ranitidine, cimetidine, grapefruit juice</p> <p>Decrease of the cyclosporine level (CYP3A induction) through: Carbamazepine, phenytoin, barbiturates, metamizole, St. John's wort</p> <p>Possible reinforcement of nephrotoxic adverse drug reactions through: Aminoglycosides, amphotericin B, ciprofloxacin, acyclovir, non-steroidal antiphlogistics</p> <p>Specific interactions: Potassium-saving substances: increased risk of hyperpotassemia</p> <p>Reduced clearance of: Digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (e.g. lovastatin), diclofenac</p>
Other	<p>Increased risk of lympho-proliferative diseases in transplant patients. Increased risk of squamous cell carcinoma in psoriasis patients following excessive phototherapy.</p> <p>Only moderately effective in and not approved for psoriatic arthritis</p> <p>Also used successfully in the therapy of chronic-inflammatory diseases in children</p>

**Instructions for application**Pre-treatment

## History

- ◆ Previous and concomitant diseases (e.g. severe infections, malignancies, renal and liver diseases), concomitant medications (see Drug Reactions)

## Questions/examination

- ◆ Examination for skin malignancies
- ◆ Indications of existing infections
- ◆ Measurement of the blood pressure at two different times

## Laboratory controls (see Table 3.5.2.2)

## Consultation

- ◆ Reliable contraception (*cave*: reduced efficacy of progesterone-containing contraceptives)
- ◆ Vaccination, susceptibility to infections [take infections seriously and, if needed, early presentation (e.g., visit GP)]
- ◆ Drug interactions (inform other treating physicians about therapy)
- ◆ Avoid excessive sun exposure, use of light-protection measures

Measures during the therapy

## Questions/examination

- ◆ Status of skin and mucous membranes (e.g., increase of body hair, gingival hyperplasia)
- ◆ Signs of infections
- ◆ Gastrointestinal or neurological symptoms
- ◆ Repeat recommendation for light avoidance and protection from sun light
- ◆ Check concomitant medications
- ◆ Measure blood pressure

## Laboratory controls (see Table 3.5.2.2)

- ◆ With an uncomplicated long-term therapy with low dose (2.5–3 mg/kg BW daily) control intervals may later be extended to 2 months
- ◆ Short intervals (e.g., in patients with risk factors), dosage increases with the intake of metabolic drugs or with regard to the ADRs of interacting drugs
- ◆ Creatinine clearance in cases of implausible creatinine plasma levels
- ◆ In selected patients with intermittent and short-term treatment, a smaller number of controls (e.g., regular controls of blood pressure and creatinine assay) may be sufficient
- ◆ Determination of the cyclosporine level is recommended in individual cases

Measures after therapy

- ◆ None

**Table 15** Laboratory controls during treatment with cyclosporine

Period in weeks → Diagnostics ↓	Before	2	4	8	12	16
Complete blood count <sup>a</sup>	x	x	x	x	x	x
Liver values <sup>b</sup>	x	x	x	x	x	x
Electrolytes <sup>c</sup>	x	x	x	x	x	x
Serum creatinine	x	x	x	x	x	x
Urea	x	x	x	x	x	x
Urinalysis and -sediment	x		x	x	x	x
Uric acid	x	x	x	x	x	
Pregnancy test (urine)	x					
Cholesterol, triglycerides <sup>d</sup>	x			x		x
Magnesium <sup>e</sup>	x			x		x

<sup>a</sup> Erythrocytes, leukocytes, platelets

<sup>b</sup> ALT, AST, AP (alkaline phosphatase),  $\gamma$ GT (gamma glutamyl transpeptidase), bilirubin

<sup>c</sup> Sodium, potassium

<sup>d</sup> Recommended twice (fasting) and week-2 and 0

<sup>e</sup> Only with indication (e.g. muscle cramps)

### General assessment

Of 65 studies evaluated with respect to the efficacy of a cyclosporine monotherapy in psoriasis, 15 studies fulfilled the Guidelines' inclusion criteria.<sup>186, 114-127</sup> Cyclosporine demonstrated a high effectiveness in the therapy of adults in these clinical studies. After 12–16 weeks, 50–70% of the patients achieved a PASI 75 (LE 1). Cyclosporine is primarily suited for induction therapy; in long-term therapy a careful and individual weighing of the risks and benefits must be performed due to the adverse drug reactions, especially the nephrotoxicity and increase in blood pressure as well as the possibility of an increased risk of malignancies.

With the application of cyclosporine, a variety of drug reactions need to be considered, which on the one hand lead to a change in the availability of cyclosporine or concomitant medications, and on the other hand might increase the risk of adverse drug reactions.

As a result of its long-term use for various indications, including psoriasis vulgaris, an extensive body of data is available – also in terms of safety during long-term therapy with cyclosporine.

Cyclosporine represents an effective therapy for moderate and severe psoriasis vulgaris.

### Therapeutic recommendation

Cyclosporine is primarily recommended for induction therapy for moderate to severe psoriasis vulgaris in adults who cannot be sufficiently treated with a topical therapy and/or phototherapy. In these cases, there is an acceptable risk-benefit ratio.

Cyclosporine can also be used for the long-term therapy of suitable patients over a period of up to 2 years maximum, whereby an increasing toxicity and a decreasing efficacy should be considered.

A combination with topical preparations for the treatment of psoriasis vulgaris is possible and reasonable, especially because there are signs that combining cyclosporine with topical vitamin D<sub>3</sub>-analogues or corticosteroids may allow a dose reduction of cyclosporine without a loss of efficacy.

### Fumaric acid esters

**Table 16** Tabular summary

Fumaric acid esters	
First approved in Germany	1995 (Psoriasis vulgaris)
Recommended control parameters	Serum creatinine, transaminases/ $\gamma$ GT, complete blood count including differential blood count, urinalysis
Recommended initial dosage	According to recommended dosage regimen see Table 17
Recommended maintenance dosage	Individually adapted dosage
Expected beginning of clinical effect	After approximately 6 weeks
Response rate	PASI 75 in 50–70% of the patients at the end of the induction phase after 16 weeks (LE 2)
Important contraindications (limited selection)	Chronic diseases of the gastrointestinal tract and/or the kidneys and chronic diseases, which are accompanied by an impairment of the leukocyte count or functions, malignant diseases, pregnancy and nursing
Important ADRs (limited selection)	Gastrointestinal complaints, flush, lymphopenia, eosinophilia
Important drug interactions	None known
Other	–

**Table 17** Dosage regimen for Fumaderm therapy

	Fumaderm initial	Fumaderm
Week 1	1-0-0	
Week 2	1-0-1	
Week 3	1-1-1	
Week 4		1-0-0
Week 5		1-0-1
Week 6		1-1-1
Week 7		2-1-1
Week 8		2-1-2
Week 9		2-2-2

**Instructions for application**

Pre-treatment

- ◆ Laboratory controls (see Table 3.5.3.3)

During treatment

- ◆ Laboratory controls (see Table 3.5.3.3)

Post-treatment

- ◆ None

**Table 18** Laboratory controls during treatment with fumaric acid esters

Period in weeks → Diagnostics ↓	Pre-treatment	Month 1–6 every 4 weeks	After month 6 every 8 weeks
Complete blood count <sup>a</sup>	x	x	x
ALT, AST, γGT	x	x	x
Serum creatinine	x	x	x
Urinalysis	x	x	x

<sup>a</sup> Leukocytes, platelets, erythrocytes, differential blood count

**General assessment**

Of 13 studies evaluated, nine fulfilled the Guidelines' inclusion criteria.<sup>[128-136]</sup> After 16 weeks, 50–70% of the patients had a PASI 75 (LE 2). There was good efficacy in the induction therapy and in the long-term therapy. The therapy of psoriasis vulgaris with fumaric acid esters represents an effective systemic treatment which demonstrates a high level of long-term safety. The tolerance is limited by adverse gastrointestinal drug reactions and flush symptoms. The risk-benefit analysis of fumaric acid esters is positive, the practicality for both patients and physicians is good, and the cost-benefit ratio is acceptable. Positive aspects of the therapy with fumaric acid esters are the low number of drug interactions, the lack of immunosuppressive effects, the absence of increased susceptibility to infection, and the absence of any risk of malignancies during the long-term therapy. A combination with topical medications for the treatment of psoriasis vulgaris is recommendable.

**Therapeutic recommendation**

Treatment with fumaric acid esters is recommended as an effective induction therapy for moderate to severe psoriasis vulgaris in adults. ↑

Their application is primarily limited by gastrointestinal ADRs. A combination with any topical drugs for the treatment of psoriasis vulgaris is possible and reasonable.

Because of the favorable risk-benefit profile with good tolerability during long-term therapy, fumaric acid esters are highly recommended. ↑↑

## Methotrexate

**Table 19** Tabular summary

Methotrexate	
First approved in Germany	
Lantarel <sup>®</sup>	1991 (Psoriasis vulgaris)
Metex <sup>®</sup> 7.5/10 mg	1992 (Psoriasis vulgaris)
Metex <sup>®</sup> 2.5 mg	2004 (Psoriasis vulgaris)
Recommended control parameters	Complete blood count (Hb, HCT, differential blood count, platelets), renal function (serum creatinine, urea, urine sediment), liver values (serum transaminases), III-procollagen amino terminal propeptides
Recommended initial dosage	5–15 mg per week
Recommended maintenance dosage	5–22.5 mg per week depending on effect
Expected beginning of clinical effect	After 4–8 weeks
Response rate	PASI 75 in approximately 60% of the patients at the end of the induction phase of 16 weeks (LE 3)
Important contraindications (limited selection)	<p><b>Absolute contraindications:</b></p> <p>Desire to have children (for both men and women), pregnancy and nursing, inadequate contraception, drug consumption, alcoholism, known sensitivity to active ingredient methotrexate (e.g. pulmonary toxicity), bone marrow dysfunction, severe liver disease, severe infections, immunodeficiency, active peptic ulcers, hematologic changes (leucopenia, thrombocytopenia, anemia), renal failure</p> <p><b>Relative contraindications:</b></p> <p>Kidney disorders, liver disorders, history of arsenic consumption, chronic congestive cardio-myopathy, adiposity, old age, diabetes mellitus, history of hepatitis, lack of patient compliance, ulcerative colitis, diarrhea, NSAID use, gastritis</p>
Important ADRs (limited selection)	Liver fibrosis/cirrhosis, pneumonia/alveolitis, bone marrow depression, renal damage, alopecia (reversible), nausea, weariness, vomiting, elevated transaminases, infection, gastrointestinal ulcerations, nephrotoxicity

**Table 19** continued

Methotrexate	
Important drug interactions (limited selection)	Cyclosporine, salicylates, sulfonamides, probenecide, penicillin, colchicin, NSAIDs (naproxene, ibuprofene, etc.), ethanol, co-trimoxazole, pyrimethamine, chloramphenicol, sulfonamides, prostaglandin synthesis inhibitors, cytostatics, probenecide, barbiturates, phenytoin, retinoids, sulfonamides, sulfonyleurea, tetracyclines, co-trimoxazol, chloramphenicol, dipyridamole, retinoids, ethanol, leflunomide
Other	Consistent avoidance of alcohol, X-ray of the lungs prior to beginning therapy

### Instructions for application

#### Pre-treatment

##### Anamnesis

- ◆ Exclusion of alcohol abuse

##### Physical examination

- ◆ Sonography of liver following indication, i.e., with a positive anamnesis or pathological findings in the physical examination
- Examine for skin signs of chronic hepatic disease

##### Laboratory controls (see Table 3.5.4.2)

- ◆ An assay of the type III procollagen amino terminal propeptide (PIIINP) in serum is recommended

##### Imaging procedures

- ◆ Chest x-ray (as necessary comparative image for the occurrence of pulmonary changes)

##### Other

- ◆ Information about intake (only on 1 day a week) and early symptoms of potential ADRs

#### During treatment

- ◆ Adequate contraceptive measures (for the treatment of both men and women)
- ◆ Laboratory controls (see Table 3.5.4.2)
- ◆ With dosage increases and an increased risk of an elevated MTX concentration (dehydration, reduced renal function, new medications) controls are performed more frequently
- ◆ An assay of type III procollagen amino terminal propeptide (PIIINP) in serum is recommended
- ◆ Liver biopsy: as soon as there is a longer treatment period following a cumulative dose of more than 1.5 g or more or if liver damage is suspected, a hepatologist should be consulted to determine whether a liver biopsy is needed<sup>473, 761</sup>
- ◆ Chest x-ray: for complaints such as fever, coughing, dyspnoea, and cyanosis; important: MTX pneumonitis
- ◆ For the general reduction of toxicity, 5 mg per day folic acid can be recommended on the days when there is no MTX intake
- ◆ Careful registration of cumulative dose

#### Post-treatment

- ◆ Reliable contraceptive measures for at least 3 months after therapy in both men and women

**Table 20** Laboratory controls during treatment with MTX [137]

Period in weeks → Diagnostics ↓	Before treatment	First month: 1x/week	2nd – 3rd month 1x/2 weeks	After 4th month every 2–3 months
Complete blood count <sup>a</sup>	x	x	x	x
Liver values <sup>b</sup>	x	x	x	x
Creatinine/urea	x	x	x	x
Urine sediment	x	x	x	x
Pregnancy test (urine)	x			
Liver sonography <sup>c</sup>	x			
Chest X-ray	x			
Hepatitis B, C serology	x			
Type III procollagen amino terminal propeptide (PIIINP)	x		then every 3 months	

<sup>a</sup> Hb, HCT, erythrocytes, leukocytes, differential blood count, platelets

<sup>b</sup> ALT, AST, AP,  $\gamma$ GT, albumin, bilirubin, lactate dehydrogenase (LDH)

<sup>c</sup> Liver biopsy instead of a liver sonography in risk groups

### General assessment

Of 11 MTX monotherapy studies assessed for efficacy in psoriasis vulgaris, three studies fulfilled the Guidelines' inclusion criteria.<sup>[123, 138, 139]</sup>

After a 16-week therapy with MTX, approximately 60–75% of the patients displayed a 75% reduction of the PASI score (LE 3). Clinical experience with MTX is much greater than the documentation of the efficacy and safety of a MTX therapy in clinical studies. Clinical experience has demonstrated that with longer treatment, the efficacy continues to increase and MTX therefore represents, above all, an effective therapeutic option for long-term therapy.

The clinical application is restricted by severe ADRs including, in particular, hepatotoxicity, nephrotoxicity, bone marrow suppression, gastrointestinal ulcerations and very rare, but severe idiosyncratic reactions.

With precise patient selection, thorough patient information, strict monitoring, administration of the lowest effective dosage (max. 22.5 mg per week) and the additional administration of folic acid or folinic acid, an acceptable safety profile can also be attained for MTX therapy.

MTX provides the lowest drug costs per day of all the systemic therapeutics.

### Therapeutic recommendation

MTX is effective in the treatment of moderate to severe psoriasis vulgaris; its use is limited by the contraindications and numerous controls needed during therapy.

MTX is, as a result of its slow onset of action, less recommendable for short-term induction therapy than for long-term therapy.





## Retinoids

**Table 21** Tabular summary

Acitretin	
First approved in Germany	1992 (Psoriasis vulgaris)
Recommended control parameters	Erythrocyte sedimentation rate (ESR), complete blood count, liver values, renal values, blood lipid values, pregnancy test, x-ray control of the bones in case of long-term therapy
Recommended initial dosage	0.3–0.5 mg/kg BW per day for approximately 4 weeks, then 0.5–0.8 mg/kg BW
Recommended maintenance dosage	Individual dosaging dependent on the results and tolerance
Expected beginning of clinical effect	After 4–8 weeks
Response rate	Widely variable and dose-dependent, no definite statement possible, partial remission (PASI 75) in 25–75% of the patients (30–40 mg per day) (LE 3) in studies
Important contraindications (limited selection)	Renal and liver damage, desire to have children in female patients of child-bearing age, pregnancy, nursing, alcohol abuse, manifest diabetes mellitus, wearing of contact lenses, history of pancreatitis, hyperlipidemia requiring drug treatment
Important ADRs (limited selection)	Hypervitaminosis A (e.g., cheilitis, xerosis, nose-bleeding, alopecia, increased skin fragility)
Important drug interactions (limited selection)	Phenytoin, tetracyclines, methotrexate, alcohol, mini-pill
Other	Contraception up to 2 years after discontinuation in female patients of child-bearing age

**Instructions for application**Pre-treatment

## Anamnesis

- ◆ Exclusion of pregnancy/nursing<sup>a</sup> (patient must be informed expressly and extensively about the teratogenic risk of the medication, the necessity of effective and long-term contraception, and the possible consequences of a pregnancy while taking retinoids); written documentation of the patient information interview
- ◆ Alcohol consumption (women of child-bearing age may not drink alcohol during and up to 2 months after treatment with acitretin)
- ◆ Exclusion of alcohol abuse
- ◆ Question regarding bone aches and aches in joints
- ◆ Laboratory controls (see Table 3.5.5.2)

During treatment

- ◆ With long-term treatment (approximately 1–2 years): radiological control examinations of the spine and joints are recommended if signs and symptoms develop to exclude possible occurrence of ossification
- ◆ Reliable contraception<sup>a</sup> in women of child-bearing age
- ◆ For women of child-bearing age: No alcohol consumption during therapy
- ◆ Laboratory controls (see Table 3.5.5.2)

Post-treatment

- ◆ Patients may not donate blood for up to 1 year after the discontinuation of therapy
- ◆ Reliable contraception<sup>a</sup> in women of child-bearing age up to 2 years after therapy
- ◆ For women of child-bearing age: no alcohol consumption up to 2 months after end of therapy

<sup>a</sup> Double contraception is recommended (e.g., condom + pill; IUD/Nuva-Ring + pill; caveat: no low-dosed progesterone preparations/mini-pills) during and up to 2 years after the end of therapy; effectiveness is reduced by acitretin

**Table 22** Laboratory controls during treatment with Acitretin

Period in weeks → Diagnostics ↓	Pre-treatment	4	8	16
Complete blood count <sup>a</sup>	x		x	x
AST, ALT, AP, yGT	x	x	x	x
Creatinine, urea	x			
Triglycerides, cholesterol, HDL <sup>b</sup>	x	x		x
Pregnancy test (urine) (monthly up to 2 years after therapy)	x	Monthly		
Fasting blood sugar	x			

<sup>a</sup> Hb, HCT, leukocytes, platelets

<sup>b</sup> Preferably assayed twice (week-2 and 0); HDL, high-density lipoprotein

**General assessment**

Of 52 studies assessed, four fulfilled the Guidelines' inclusion criteria in terms of a monotherapy and another four in terms of a combination therapy.<sup>[91-93, 140-143]</sup>

As a result of the very heterogeneous study results, it is not possible to make a clear statement regarding the efficacy of a monotherapy with acitretin (LE 3).


The effectiveness of retinoids in lower dosages as a monotherapy in moderate to severe psoriasis vulgaris is not satisfactory.

Higher dosages result in an increase of the efficacy, but these are frequently accompanied by increased ADRs in the skin and mucous membranes.


In women of childbearing age, the teratogenicity, the monthly pregnancy tests, and the need for contraception for up to 2 years after the termination of the therapy severely limit the use of acitretin.

An advantage of treatment with retinoids is the synergistic effect in combination with UV light. There is, however, insufficient evidence available on the basis of the studies included to recommend this approach.

**Therapeutic recommendation**

Acitretin is not recommended as a monotherapy because of lack of efficacy. 

The application of higher dosages, which are more effective, is limited because of frequent adverse drug reactions.

The treatment of plaque psoriasis with acitretin in women of child-bearing age is strongly discouraged. 

**Other therapies**

*Climate/balneotherapy*

**Table 23** Tabular summary

Climate/balneotherapy	
First approved in Germany	Clinical experience with balneotherapy has existed for more than 200 years
Recommended control parameters	Regular skin inspection
Recommended initial dosage	Therapy regimens vary depending on the institution/location
Recommended maintenance dosage	Therapy regimens vary depending on the institution/location
Expected beginning of clinical effect	Varies greatly
Response rate	Varies greatly (LE 4)
Important contraindications	Dependent on modality selected
Important ADRs	Dependent on modality selected
Important drug interactions	Not applicable
Other	Balneotherapy and climate therapy are frequently combined

**General assessment**

Of 33 studies assessed, three fulfilled the Guidelines' inclusion criteria.<sup>[144-146]</sup> This translates into a level of evidence 4.

The onset of clinical effect and the response rate vary greatly. For that reason, it is not possible to provide exact figures.

Balneotherapy and climate therapy have been successfully applied for the treatment of psoriasis vulgaris for centuries and are frequently used in combination with other therapies.


These are treatment modalities which have been developed over the years, but for which only very preliminary scientific data are available.

In the case of a combined strategy using natural phototherapeutic principles, efficacy and safety are similar to those of simple phototherapy.

Balneotherapy and climate therapy are tied to certain geographic regions and the specialized facilities located there.

**Therapeutic recommendation**

Balneotherapy and climate therapy have a special place in the framework of the long-term management of psoriasis vulgaris.

The integration of appropriate therapy phases into the treatment concept of patients with psoriasis vulgaris requiring treatment for years can be recommended. 

These methods are not indicated for acute treatment or short-term therapy.

## Psychosocial therapy

**General assessment**

Of eight studies evaluated, three fulfilled the Guidelines' inclusion criteria.<sup>[77, 147, 148]</sup> This resulted in a level of evidence 4.

These studies of an additive, psychosocial treatment of psoriasis patients with the evidence grade B or C and with a large random sample selection as well as a relatively large dropout rates do not allow for any final conclusions to be drawn with respect to the efficacy of these therapies.

The low number of adverse events is certainly an advantage.

With a psychosocial treatment like Psoriasis Symptom Management or patient training, direct effects on skin symptoms can be achieved through, for example, improved stress management, and indirect effects on the development of the psoriasis can be achieved through, for example, improved compliance.

These two forms of therapy should be further investigated empirically.

**Therapeutic recommendation**

The possible impacts of the disease on social, emotional and psychic aspects should be considered for every psoriatic patient.



Information on existing self-help groups is recommended.



The possibility of participating in a structured training program in accordance with the recommendations of the ADP (Arbeitsgemeinschaft Dermatologische Prävention) of the DDG should be pointed out.



If the suffering is very intense or in cases of repeated clear exacerbation of the psoriasis vulgaris with stress, evaluation by an appropriate specialist with training in psychosomatics or psychotherapy can be offered if the patient so desires and, if necessary, psychosocial therapy initiated.

**Notes on the use of the Guidelines**

The presentation of the therapies deliberately focused on those aspects deemed particularly relevant by a panel of experts. Aspects which are not of specific importance for a certain intervention, but which are part of the physician's general obligations to the patient, such as the investigation of intolerance and allergies toward certain drugs or the exclusion of contraindications, are not individually listed, but it is nevertheless taken for granted that these are part of the physician's duty to provide care.

It is recommended that each and every user carefully reads and follows the product information and compare it with the recommendations in the Guidelines on dosaging, contraindications, and drug interactions for completeness and currentness. Every dose or application is administered at the user's own risk. The authors and the publishers kindly request that users inform them of any inaccuracies that they might notice. The users are requested to keep themselves constantly informed of any new findings subsequent to the publication of the Guidelines.

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**References**

1. Richards HL, Fortune DG, O'Sullivan TM, Main CJ, Griffiths CE (1999) Patients with psoriasis and their compliance with medication. *J Am Acad Dermatol* 41(4):581–583
2. Nevitt GJ, Hutchinson PE (1996) Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. *Br J Dermatol* 135(4):533–537
3. Schmid-Ott G, Malewski P, Kreislermaier I, Mrowietz U (2005) Psychosoziale Folgen der Psoriasis—eine empirische Studie über die Krankheitslast bei 3753 Betroffenen. *Hautarzt* 56(5):466–472
4. Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM (1999) Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 41(3 Pt 1): 401–407
5. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T (2004) Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Invest Dermatol Symp Proc* 9(2):136–139
6. Carroll CL, Clarke J, Camacho F, Balkrishnan R, Feldman SR (2005) Topical tacrolimus ointment combined with 6% salicylic acid gel for plaque psoriasis treatment. *Arch Dermatol* 141(1):43–46

7. Agarwal R, Saraswat A, Kaur I, Katare OP, Kumar B (2002) A novel liposomal formulation of dithranol for psoriasis: preliminary results. *J Dermatol* 29(8):529–532
8. Monastirli A, Georgiou S, Pasmatzis E, Sakkis T, Badavanis G, Drinas D, Sagriotis A, Tsambaos D (2002) Calcipotriol plus short-contact dithranol: a novel topical combination therapy for chronic plaque psoriasis. *Skin Pharmacol Appl Skin Physiol* 15(4):246–251
9. Gerritsen MJ, Boezeman JB, Elbers ME, van de Kerkhof PC (1998) Dithranol embedded in crystalline monoglycerides combined with phototherapy (UVB): a new approach in the treatment of psoriasis. *Skin Pharmacol Appl Skin Physiol* 11(3):133–139
10. Prins M, Swinkels OQ, Van de Kerkhof PC, Van der Valk PG (2001) The impact of the frequency of short contact dithranol treatment. *Eur J Dermatol* 11(3):214–218
11. Thune P, Brolund L (1992) Short- and long-contact therapy using a new dithranol formulation in individually adjusted dosages in the management of psoriasis. *Acta Derm Venereol Suppl* 172:28–29
12. De Mare S, Calis N, den Hartog G, van Erp PE, van de Kerkhof PC (1988) The relevance of salicylic acid in the treatment of plaque psoriasis with dithranol creams. *Skin Pharmacol* 1(4):259–264
13. Prins M, Swinkels OQ, Bouwhuis S, de Gast MJ, Bouwman-Boer Y, van der Valk PG, van de Kerkhof PC (2000) Dithranol in a cream preparation: disperse or dissolve? *Skin Pharmacol Appl Skin Physiol* 13(5):273–279
14. Hutchinson PE, Marks R, White J (2000) The efficacy, safety and tolerance of calcitriol 3 microg/g ointment in the treatment of plaque psoriasis: a comparison with short-contact dithranol. *Dermatology* 201(2):139–145
15. Mahrle G, Schulze HJ (1990) The effect of initial external glucocorticoid administration on cignolin treatment of psoriasis. *Z Hautkr* 65(3):282, 285–287
16. Agrup G, Agdell J (1985) A comparison between Antraderm stick (0.5% and 1%) and dithranol paste (0.125% and 0.25%) in the treatment of psoriasis. *Br J Clin Pract* 39(5):185–187
17. Swinkels OQ, Prins M, Kucharekova M, de Boo T, Gerritsen MJ, van der Valk PG, van de Kerkhof PC (2002) Combining lesional short-contact dithranol therapy of psoriasis with a potent topical corticosteroid. *Br J Dermatol* 146(4):621–626
18. Gottlieb AB, Ford R, Spellman MC (2003) The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type psoriasis of nonscalp regions. *J Cutan Med Surg* 7(3):185–192
19. Chuang TY, Samson CR (1991) Clinical efficacy and safety of augmented betamethasone dipropionate ointment and diflorasone ointment for psoriasis—a multicentre, randomized, double-blinded study. *J Dermatol Treat* 2(2):63–66
20. Katz HI, Tanner DJ, Cuffie CA, Brody NI, Garcia CJ, Lowe NJ, Medansky RS, Roth HL, Shavin JS, Swinyer LJ (1998) A comparison of the efficacy and safety of the combination mometasone furoate 0.1%/salicylic acid 5% ointment with each of its components in psoriasis. *J Dermatol Treat* 9(3):151–156
21. Koo J, Cuffie CA, Tanner DJ, Bressinck R, Cornell RC, DeVillez RL, Edwards L, Breneman DL, Piacquadio DJ, Guzzo CA, Monroe EW (1998) Mometasone furoate 0.1%–salicylic acid 5% ointment versus mometasone furoate 0.1% ointment in the treatment of moderate-to-severe psoriasis: a multicenter study. *Clin Ther* 20(2):283–291
22. Camarasa JM, Ortonne JP, Dubertret L (2003) Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. *J Dermatol Treat* 14(1):8–13
23. Papp KA, Guenther L, Boyden B, Larsen FG, Harvima RJ, Guilhou JJ, Kaufmann R, Rogers S, van de Kerkhof PC, Hanssen LI, Tegner E, Burg G, Talbot D, Chu A (2003) Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. *J Am Acad Dermatol* 48(1):48–54
24. Douglas WS, Poulin Y, Decroix J, Ortonne JP, Mrowietz U, Gulliver W, Krogstad AL, Larsen FG, Iglesias L, Buckley C, Bibby AJ (2002) A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. *Acta Derm Venereol* 82(2):131–135
25. Kaufmann R, Bibby AJ, Bissonnette R, Cambazard F, Chu AC, Decroix J, Douglas WS, Lowson D, Mascaro JM, Murphy GM, Szymne B (2002) A new calcipotriol/betamethasone dipropionate formulation (Daivobet) is an effective once-daily treatment for psoriasis vulgaris. *Dermatology* 205(4):389–393
26. Stein LF, Sherr A, Solodkina G, Gottlieb AB, Chaudhari U (2001) Betamethasone valerate foam for treatment of nonscalp psoriasis. *J Cutan Med Surg* 5(4):303–307
27. Decroix J, Pres H, Tsankov N, Poncet M, Arsonnaud S (2004) Clobetasol propionate lotion in the treatment of moderate to severe plaque-type psoriasis. *Cutis* 74(3):201–206
28. Lebwohl M, Sherer D, Washenik K, Krueger GG, Menter A, Koo J, Feldman SR (2002) A randomized, double-blind, placebo-controlled study of clobetasol propionate 0.05% foam in the treatment of nonscalp psoriasis. *Int J Dermatol* 41(5):269–274
29. Peharda V, Gruber F, Prpic L, Kastelan M, Brajac I (2000) Comparison of mometasone furoate 0.1% ointment and betamethasone dipropionate 0.05% ointment in the treatment of psoriasis vulgaris. *Acta Derm Venereol Croat* 8(4):223–226
30. Shupack JL, Jondreau L, Kenny C, Stiller MJ (1993) Diflorasone diacetate ointment 0.05% versus betamethasone dipropionate ointment 0.05% in moderate-severe plaque-type psoriasis. *Dermatology* 186(2):129–132
31. Svensson ARI, Gisslen H, Nordin P, Gios I (1992) A comparative study of mometasone furoate ointment and betamethasone valerate ointment in patients with Psoriasis vulgaris. *Curr Ther Res Clin Exp* 52(3):390–396
32. Weston WL, Fennessey PV, Morelli J, Schwab H, Mooney J, Samson C, Huff L, Harrison LM, Gotlin R (1988) Comparison of hypothalamus-pituitary-adrenal axis suppression from superpotent steroids by standard endocrine function testing and gas chromatographic mass spectrometry. *J Invest Dermatol* 90(4):532–535
33. Medansky RS, Cuffie CA, Tanner DJ (1997) Mometasone furoate 0.1%–salicylic acid 5% ointment twice daily versus fluocinonide 0.05% ointment twice daily in the management of patients with psoriasis. *Clin Ther* 19(4):701–709
34. Housman TS, Keil KA, Mellen BG, McCarty MA, Fleischer AB Jr, Feldman SR (2003) The use of 0.25% zinc pyrithione spray does not enhance the efficacy of clobetasol propionate 0.05% foam in the treatment of psoriasis. *J Am Acad Dermatol* 49(1):79–82
35. Bagatell F (1988) Management of psoriasis: a clinical evaluation of the dermatological patch, Actiderm registered trade mark, over a topical steroid. *Adv Ther* 5(6):291–296
36. Fabry H, Yawalkar SJ (1983) A comparative multicentre trial of halometasone ointment and fluocortolone plus fluocortolone caproate ointment in the treatment of psoriasis. *J Int Med Res* 11(Suppl 1):26–30
37. Belsito DV, Kechijian P (1982) The role of tar in Goeckerman therapy. *Arch Dermatol* 118(5): 319–321

38. Diette KM, Momtaz K, Stern RS, Arndt KA, Parrish JA (1984) Role of ultraviolet A in phototherapy for psoriasis. *J Am Acad Dermatol* 11(3):441–447
39. LeVine MJ, Parrish JA (1982) The effect of topical fluocinonide ointment on phototherapy of psoriasis. *J Invest Dermatol* 78(2):157–159
40. Frost P, Horwitz SN, Caputo RV, Berger SM (1979) Tar gel-phototherapy for psoriasis. Combined therapy with suberythemogenic doses of fluorescent sunlamp ultraviolet radiation. *Arch Dermatol* 115(7):840–846
41. Weinstein GD, Koo JY, Krueger GG, Lebwohl MG, Lowe NJ, Menter MA, Lew-Kaya DA, Sefton J, Gibson JR, Walker PS (2003) Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. *J Am Acad Dermatol* 48(5):760–767
42. Gollnick H, Menter A (1999) Combination therapy with tazarotene plus a topical corticosteroid for the treatment of plaque psoriasis. *Br J Dermatol* 140(Suppl 54):18–23
43. Green L, Sadoff W (2002) A clinical evaluation of tazarotene 0.1% gel, with and without a high- or mid-high-potency corticosteroid, in patients with stable plaque psoriasis. *J Cutan Med Surg* 6(2):95–102
44. Koo JY, Martin D (2001) Investigator-masked comparison of tazarotene gel q.d. plus mometasone furoate cream q.d. vs. mometasone furoate cream b.i.d. in the treatment of plaque psoriasis. *Int J Dermatol* 40(3):210–212
45. Lebwohl M (2000) Strategies to optimize efficacy, duration of remission, and safety in the treatment of plaque psoriasis by using tazarotene in combination with a corticosteroid. *J Am Acad Dermatol* 43(2 Pt 3):S43–S46
46. Poulin YP (1999) Tazarotene 0.1% gel in combination with mometasone furoate cream in plaque psoriasis: a photographic tracking study. *Cutis* 63(1):41–48
47. Van de Kerkhof PC, Green C, Hamberg KJ, Hutchinson PE, Jensen JK, Kidson P, Kragballe K, Larsen FG, Munro CS, Tillman DM (2002) Safety and efficacy of combined high-dose treatment with calcipotriol ointment and solution in patients with psoriasis. *Dermatology* 204(3):214–221
48. Guenther L, Van de Kerkhof PC, Snellman E, Kragballe K, Chu AC, Tegner E, Garcia-Diez A, Springborg J (2002) Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial. *Br J Dermatol* 147(2):316–323
49. Kragballe K, Noerrelund KL, Lui H, Ortonne JP, Wozel G, Uurasmaa T, Fleming C, Estebarez JL, Hanssen LI, Persson LM (2004) Efficacy of once-daily treatment regimens with calcipotriol/betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris. *Br J Dermatol* 150(6):1167–1173
50. Ortonne JP, Kaufmann R, Lecha M, Goodfield M (2004) Efficacy of treatment with calcipotriol/betamethasone dipropionate followed by calcipotriol alone compared with tacalcitol for the treatment of psoriasis vulgaris: a randomised, double-blind trial. *Dermatology* 209(4):308–313
51. Guenther LC, Poulin YP, Pariser DM (2000) A comparison of tazarotene 0.1% gel once daily plus mometasone furoate 0.1% cream once daily versus calcipotriene 0.005% ointment twice daily in the treatment of plaque psoriasis. *Clin Ther* 22(10):1225–1238
52. Lebwohl M, Yoles A, Lombardi K, Lou W (1998) Calcipotriene ointment and halobetasol ointment in the long-term treatment of psoriasis: effects on the duration of improvement. *J Am Acad Dermatol* 39(3):447–450
53. Diette KM, Momtaz TK, Stern RS, Arndt KA, Parrish JA (1984) Psoralens and UV-A and UV-B twice weekly for the treatment of psoriasis. *Arch Dermatol* 120(9):1169–1173
54. Ramsay CA, Schwartz BE, Lawson D, Papp K, Bolduc A, Gilbert M (2000) Calcipotriol cream combined with twice weekly broad-band UVB phototherapy: a safe, effective and UVB-sparing antipsoriatic combination treatment. The Canadian Calcipotriol and UVB Study Group. *Dermatology* 200(1):17–24
55. Ring J, Kowalzik L, Christophers E, Schill WB, Schopf E, Stander M, Wolff HH, Altmeyer P (2001) Calcitriol 3 microg g<sup>-1</sup> ointment in combination with ultraviolet B phototherapy for the treatment of plaque psoriasis: results of a comparative study. *Br J Dermatol* 144(3):495–499
56. Petrozzi JW (1983) Topical steroids and UV radiation in psoriasis. *Arch Dermatol* 119(3):207–210
57. Coven TR, Burack LH, Gilleaudeau R, Keogh M, Ozawa M, Krueger JG (1997) Narrowband UV-B produces superior clinical and histopathological resolution of moderate-to-severe psoriasis in patients compared with broadband UVB. *Arch Dermatol* 133:514–522
58. Snellman E, Klimenko T, Rantanen T (2004) Randomized half-side comparison of narrowband UVB and trimethylpsoralen bath. *Acta Derm Venereol* 84(2):132–137
59. Gordon PM, Diffey BL, Matthews JNS, Farr PM (1999) A randomised comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *J Am Acad Dermatol* 41:728–732
60. Leenutaphong V, Nimkulrat P, Sudtim S (2000) Comparison of phototherapy two times and four times a week with low doses of narrow-band ultraviolet B in Asian patients with psoriasis. *Photodermatol Photoimmunol Photomed* 16(5):202–206
61. Grundmann-Kollmann M, Ludwig R, Zollner TM, Ochsendorf F, Thaci D, Boehncke WH, Krutmann J, Kaufmann R, Podda M (2004) Narrowband UVB and cream psoralen-UVA combination therapy for plaque-type psoriasis. *J Am Acad Dermatol* 50(5):734–739
62. Katugampola GA, Rees AM, Lanigan SW (1995) Laser treatment of psoriasis. *Br J Dermatol* 133(6):909–913
63. Housman TS, Pearce DJ, Feldman SR (2004) A maintenance protocol for psoriasis plaques cleared by the 308 nm excimer laser. *J Dermatol Treat* 15(2):94–97
64. Trehan M, Taylor CR (2002) Medium-dose 308-nm excimer laser for the treatment of psoriasis. *J Am Acad Dermatol* 47(5):701–708
65. Feldman SR, Mellen BG, Housman TS, Fitzpatrick RE, Geronemus RG, Friedman PM, Vasily DB, Morison WL (2002) Efficacy of the 308-nm excimer laser for treatment of psoriasis: results of a multicenter study. *J Am Acad Dermatol* 46(6):900–906
66. Parrish JA, Fitzpatrick TB, Tannenbaum L, Pathak MA (1974) Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. *N Engl J Med* 291:1207–1211
67. Kirby B, Buckley DA, Rogers S (1999) Large increments in psoralen-ultraviolet A (PUVA) therapy are unsuitable for fair-skinned individuals with psoriasis. *Br J Dermatol* 140(4):661–666
68. Buckley DA, Healy E, Rogers S (1995) A comparison of twice-weekly MPD-PUVA and three times-weekly skin typing-PUVA regimens for the treatment of psoriasis. *Br J Dermatol* 133(3):417–422
69. Berg M, Ros AM (1994) Treatment of psoriasis with psoralens and ultraviolet A. A double-blind comparison of 8-methoxy-



- soralen and 5-methoxypsoralen. *Photodermatol Photoimmunol Photomed* 10:217–220
70. Cooper EJ, Herd RM, Priestley GC, Hunter JA (2000) A comparison of bathwater and oral delivery of 8-methoxypsoralen in PUVA therapy for plaque psoriasis. *Clin Exp Dermatol* 25(2):111–114
  71. Collins P, Rogers S (1992) Bath-water compared with oral delivery of 8-methoxypsoralen PUVA therapy for chronic plaque psoriasis. *Br J Dermatol* 127(4):392–395
  72. Calzavara-Pinton PG, Ortel B, Honigsman H, Zane C, De Panfilis G (1994) Safety and effectiveness of an aggressive and individualized bath-PUVA regimen in the treatment of psoriasis. *Dermatology* 189(3):256–259
  73. Barth J, Dietz O, Heilmann S, Kadner H, Kraensel H, Meffert H, Metz D, Pinzer B, Schiller F (1978) Fotochemotherapie mit 8-methoxypsoralen und UVA bei Psoriasis vulgaris. *Dermatol Monatsschr* 164(6):401–407
  74. Khurshid K, Haroon TS, Hussain I, Pal SS, Jahangir M, Zaman T (2000) Psoralen-ultraviolet A therapy vs. psoralen-ultraviolet B therapy in the treatment of plaque-type psoriasis: our experience with Fitzpatrick skin type IV. *Int J Dermatol* 39(11):865–867
  75. Arnold WP, van Andel P, de Hoop D, de Jong-Tieben L, Visser-van Andel M (2001) A comparison of the effect of narrow-band ultraviolet B in the treatment of psoriasis after salt-water baths and after 8-methoxypsoralen baths. *Br J Dermatol* 145(2):352–354
  76. Park YK, Kim HJ, Koh YJ (1988) Combination of photochemotherapy (PUVA) and ultraviolet B (UVB) in the treatment of psoriasis vulgaris. *J Dermatol* 15(1): 68–71
  77. Kabat-Zinn J, Wheeler E, Light T, Skillings A, Scharf MJ, Cropley TG, Hosmer D, Bernhard JD (1998) Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). *Psychosom Med* 60(5):625–632
  78. Frappaz A, Thivolet J (1993) Calcipotriol in combination with PUVA: a randomized double blind placebo study in severe psoriasis. *Eur J Dermatol* 3:351–354
  79. Rogers S, Marks J, Shuster S, Briffa DV, Warin A, Greaves M (1979) Comparison of photochemotherapy and dithranol in the treatment of chronic plaque psoriasis. *Lancet* 1(8114):455–458
  80. Vella Briffa D, Rogers S, Greaves MW, Marks J, Shuster S, Warin AP (1978) A randomized, controlled clinical trial comparing photochemotherapy with dithranol in the initial treatment of chronic plaque psoriasis. *Clin Exp Dermatol* 3(4):339–347
  81. Parker S, Coburn P, Lawrence C, Marks J, Shuster S (1984) A randomized double-blind comparison of PUVA-etretinate and PUVA-placebo in the treatment of chronic plaque psoriasis. *Br J Dermatol* 110(2):215–220
  82. Dover JS, McEvoy MT, Rosen CF, Arndt KA, Stern RS (1989) Are topical corticosteroids useful in phototherapy for psoriasis? *J Am Acad Dermatol* 20(5 Pt 1):748–754
  83. Hanke CW, Steck WD, Roenigk HH Jr (1979) Combination therapy for psoriasis. Psoralens plus long-wave ultraviolet radiation with betamethasone valerate. *Arch Dermatol* 115(9):1074–1077
  84. Koo JY, Lowe NJ, Lew-Kaya DA, Vasilopoulos AI, Lue JC, Sefton J, Gibson JR (2000) Tazarotene plus UVB phototherapy in the treatment of psoriasis. *J Am Acad Dermatol* 43(5 Pt 1):821–828
  85. McBride SR, Walker P, Reynolds NJ (2003) Optimizing the frequency of outpatient short-contact dithranol treatment used in combination with broadband ultraviolet B for psoriasis: a randomized, within-patient controlled trial. *Br J Dermatol* 149(6):1259–1265
  86. Levell NJ, Shuster S, Munro CS, Friedmann PS (1995) Remission of ordinary psoriasis following a short clearance course of cyclosporin. *Acta Derm Venereol* 75(1):65–69
  87. Petzelbauer P, Honigsman H, Langer K, Anegg B, Strohal R, Tanew A, Wolff K (1990) Cyclosporin A in combination with photochemotherapy (PUVA) in the treatment of psoriasis. *Br J Dermatol* 123(5):641–647
  88. Franchi C, Cainelli G, Frigerio E, Garutti C, Altomare GF (2004) Association of cyclosporine and 311 nm UVB in the treatment of moderate to severe forms of psoriasis: a new strategic approach. *Int J Immunopathol Pharmacol* 17(3):401–406
  89. Paul BS, Momtaz K, Stern RS, Arndt KA, Parrish JA (1982) Combined methotrexate-ultraviolet B therapy in the treatment of psoriasis. *J Am Acad Dermatol* 7(6):758–762
  90. Morison WL, Momtaz K, Parrish JA, Fitzpatrick TB (1982) Combined methotrexate-PUVA therapy in the treatment of psoriasis. *J Am Acad Dermatol* 6(1):46–51
  91. Caca-Biljanovska NG, V'Lckova-Laskoska MT (2002) Management of guttate and generalized psoriasis vulgaris: prospective randomized study. *Croat Med J* 43(6): 707–712
  92. Saurat JH, Geiger JM, Amblard P, Beau J-C, Boulanger A, Claudy A et al (1988) Randomized double-blind multicenter study comparing acitretin-PUVA and placebo-PUVA in the treatment of severe psoriasis. *Dermatologica* 177:218–224
  93. Lauharanta J, Geiger JM (1989) A double-blind comparison of acitretin and etretinate in combination with bath PUVA in the treatment of extensive psoriasis. *Br J Dermatol* 121(1):107–112
  94. Orfanos CE, Steigleder GK, Pullmann H, Bloch PH (1979) Oral retinoid and UVB radiation: a new, alternative treatment for psoriasis on an out-patient basis. *Acta Derm Venereol* 59(3):241–244
  95. Calzavara-Pinton P (1998) Narrow band UVB (311 nm) phototherapy and PUVA photochemotherapy: a combination. *J Am Acad Dermatol* 38(5 Pt 1):687–690
  96. Markham T, Rogers S, Collins P (2003) Narrowband UV-B (TL-01) phototherapy vs oral 8-methoxypsoralen psoralen-UV-A for the treatment of chronic plaque psoriasis. *Arch Dermatol* 139(3):325–328
  97. Calzavara-Pinton P, Ortel B, Carlino A, Honigsman H, De Panfilis G (1992) A reappraisal of the use of 5-methoxypsoralen in the therapy of psoriasis. *Exp Dermatol* 1(1):46–51
  98. Henseler T, Wolff K, Honigsman H, Christophers E (1981) Oral 8-methoxypsoralen photochemotherapy of psoriasis. The European PUVA Study: a cooperative study among 18 European centres. *Lancet* 11:853–857
  99. Torras H, Aliaga A, Lopez-Estebarez JL, Hernandez I, Gardeazabal J, Quintanilla E, Mascaro JM (2004) A combination therapy of calcipotriol cream and PUVA reduces the UVA dose and improves the response of psoriasis vulgaris. *J Dermatol Treat* 15(2):98–103
  100. Hacker SM, Rasmussen JE (1992) The effect of flash lamp-pulsed dye laser on psoriasis. *Arch Dermatol* 128(6):853–855
  101. Gordon KB, Papp KA, Hamilton TK, Walicke PA, Dummer W, Li N, Bresnahan BW, Menter A (2003) Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* 290(23):3073–3080
  102. Lebwohl M, Tyring SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, Walicke P, Dummer W, Wang X, Garovoy MR, Pariser D (2003) A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 349(21):2004–2013
  103. Leonardi CL, Papp KA, Gordon KB, Menter A, Feldman SR, Caro I, Walicke PA, Compton PG, Gottlieb AB (2005) Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial. *J Am Acad Dermatol* 52(3 Pt 1):425–433



104. Menter A, Gordon K, Carey W, Hamilton T, Glazer S, Caro I, Li N, Gulliver W (2005) Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. *Arch Dermatol* 141(1):31–38
105. Papp K, Bissonnette R, Krüger JG, Carey W, Gratton D, Gulliver WP, Lui H (2001) The treatment of moderate to severe psoriasis with a new anti-CD11a monoclonal antibody. *J Am Acad Dermatol* 45(5):665–674
106. Gottlieb AB, Gordon KB, Lebwohl MG, Caro I, Walicke PA, Li N, Leonardi CL (2004) Extended efalizumab therapy sustains efficacy without increasing toxicity in patients with moderate to severe chronic plaque psoriasis. *J Drugs Dermatol* 3(6):614–624
107. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, Gaspari AA, Ling M, Weinstein GD, Nayak A, Gordon KB, Zitnik R (2003) A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol* 139(12):1627–1632; discussion 1632
108. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB (2003) Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 349(21):2014–2022
109. Costanzo A, Mazzotta A, Papoutsaki M, Nistico S, Chimenti S (2005) Safety and efficacy study on etanercept in patients with plaque psoriasis. *Br J Dermatol* 152(1):187–189
110. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, Zhou B, Dooley LT, Kavanaugh A (2005) Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 64(8):1150–1157
111. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, Bala M, Marano CW, Menter A (2004) Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 51(4):534–542
112. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB (2001) Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet* 357(9271):1842–1847
113. Schopf RE, Aust H, Knop J (2002) Treatment of psoriasis with the chimeric monoclonal antibody against tumor necrosis factor alpha, infliximab. *J Am Acad Dermatol* 46(6):886–891
114. Koo J (1998) A randomized, double-blind study comparing the efficacy, safety and optimal dose of two formulations of cyclosporin, Neoral and Sandimmun, in patients with severe psoriasis. OLP302 Study Group. *Br J Dermatol* 139(1):88–95
115. Thaci D, Brautigam M, Kaufmann R, Weidinger G, Paul C, Christophers E (2002) Body-weight-independent dosing of cyclosporine micro-emulsion and three times weekly maintenance regimen in severe psoriasis. A randomised study. *Dermatology* 205(4):383–388
116. Mahrle G, Schulze HG, Färber L, Weidinger G, Steigleder GK (1995) Low-dose short-term cyclosporine versus etretinate in psoriasis: improvement of skin, nail and joint involvement. *J Am Acad Dermatol* 32(1):78–88
117. Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, Howland Hartley A (1991) Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med* 324:277–284
118. Elder C, Moore M, Chang CT, Jin J, Charnick S, Nedelman J, Cohen A, Guzzo C, Lowe N, Simpson K (1995) Efficacy and pharmacokinetics of two formulations of cyclosporine in patients with psoriasis. *J Clin Pharmacol* 35:865–875
119. Engst R, Huber J (1989) Ergebnisse einer Cyclosporinbehandlung bei schwerer, chronischer Psoriasis vulgaris. *Hautarzt* 40:186–189
120. Laburte C, Grossman R, Abi-Rached J, Abeywickrama KM, Dubertret L (1994) Efficacy and safety of oral cyclosporine A (CYA; Sandimmun) for long-term treatment of chronic severe plaque psoriasis. *Br J Dermatol* 130:366–375
121. Meffert H, Braeutigam M, Faerber L, Weidinger G (1997) Low-dose (1,25mg/kg) cyclosporine A: treatment of psoriasis and investigation of the influence on lipid profile. *Acta Derm Venereol Suppl* 77:137–141
122. Finzi AF, Mozzanica N, Pigatto PD, Cattaneo A, Ippolito F (1993) Cyclosporine versus etretinate: Italian multicentre comparative trial in severe psoriasis. *Dermatology* 187(Suppl 1):8–18
123. Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, Bossuyt PM, Bos JD, de Rie MA (2003) Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med* 349(7):658–665
124. Reitamo S, Spuls P, Sassolas B, Lahfa M, Claudy A, Griffiths CE (2001) Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 145(3):438–445
125. Grossman RM, Thivolet J, Claudy A, Souteyrand P, Guilhou JJ, Thomas P, Amblard P, Belaich S, de Belilovsky C, de la Brassinne M et al (1994) A novel therapeutic approach to psoriasis with combination calcipotriol ointment and very low-dose cyclosporine: results of a multicenter placebo-controlled study. *J Am Acad Dermatol* 31(1):68–74
126. Finzi AF, Mozzanica N, Cattaneo A, Chiappino G, Pigatto PD (1989) Effectiveness of cyclosporine treatment in severe psoriasis: A clinical and immunologic study. *J Am Acad Dermatol* 21:91–97
127. Higgins E, Munro C, Marks J, Friedmann PS, Shuster S (1989) Relapse rates in moderately severe chronic psoriasis treated with cyclosporine A. *Br J Dermatol* 121:71–74
128. Litjens NH, Nibbering PH, Barrois AJ, Zomerdijk TP, Van Den Oudenrijn AC, Noz KC, Rademaker M, Van De Meide PH, Van Dissel JT, Thio B (2003) Beneficial effects of fumarate therapy in psoriasis vulgaris patients coincide with downregulation of type 1 cytokines. *Br J Dermatol* 148(3):444–451
129. Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, Wassilew SW, Horn T, Kreysel HW, Lutz G, Barth J, Rietzschel I, Joshi R (1994) Antipsoriatic effect of fumaric acid derivatives. Results of a multicentre double-blind study in 100 patients. *J Am Acad Dermatol* 30(6):977–981
130. Gollnick H, Altmeyer P, Kaufmann R, Ring J, Christophers E, Pavel S, Ziegler J (2002) Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. *Dermatology* 205(1):46–53
131. Kolbach DN, Nieboer C (1992) Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. *J Am Acad Dermatol* 27(5 Pt 1):769–771
132. Nugteren-Huying WM, Schroeffer JGvd, Hermans J, Suurmond D (1990) Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol* 22:311–312
133. Altmeyer P, Hartwig R, Matthes U (1996) Das Wirkungs- und Sicherheitsprofil von Fumarsäureestern in der oralen Langzeittherapie bei schwerer therapieresistenter Psoriasis vulgaris. Eine Untersuchung an 83 Patienten. *Hautarzt* 47(3):190–196
134. Bayard W, Hunziker T, Krebs A, Speiser P, Joshi R (1987) Peroral long-term treatment of psoriasis using fumaric acid derivative. *Hautarzt* 38(5):279–285
135. Carboni I, De Felice C, De Simoni I, Soda R, Chimenti S (2004) Fumaric acid esters in the treatment of psoriasis: an Italian experience. *J Dermatol Treat* 15(1):23–26

136. Mrowietz U, Christophers E, Altmeyer P (1998) Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. *Br J Dermatol* 138(3):456–460
137. Roenigk HH Jr, Auerbach R, Maibach H, Weinstein G, Leibold M (1998) Methotrexate in psoriasis: consensus conference. *J Am Acad Dermatol* 38(3):478–485
138. Weinstein GD, Frost P (1971) Methotrexate for psoriasis. A new therapeutic schedule. *Arch Dermatol* 103:33–38
139. Nyfors A, Brodthagen H (1970) Methotrexate for psoriasis in weekly oral doses without any adjunctive therapy. *Dermatologica* 140:345–355
140. van de Kerkhof PC, Cambazard F, Hutchinson PE, Haneke E, Wong E, Souteyrand P, Damstra RJ, Combemale P, Neumann MH, Chalmers RJ, Olsen L, Revuz J (1998) The effect of addition of calcipotriol ointment (50 micrograms/g) to acitretin therapy in psoriasis. *Br J Dermatol* 138(1):84–89
141. Kragballe K, Jansen CT, Geiger JM, Bjerke JR, Falk ES, Gip L, Hjorth N, Lauharanta J, Mork NJ, Reunala T et al (1989) A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of a Nordic multicentre study *Acta Derm Venereol* 69(1):35–40
142. Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ (1989) Side-effect profile of acitretin therapy in psoriasis. *J Am Acad Dermatol* 20(6):1088–1093
143. Carlin CS, Callis KP, Krueger GG (2003) Efficacy of acitretin and commercial tanning bed therapy for psoriasis. *Arch Dermatol* 139(4):436–442
144. Halevy S, Giryas H, Friger M, Sukenik H (1997) Dead sea bath salt for the treatment of psoriasis vulgaris: a double-blind controlled study. *J Eur Acad Dermatol Venereol* 9(3):237–242
145. Robertson DB, McCarty JR, Jarratt M (1978) Treatment of psoriasis with 8-methoxypsoralen and sunlight. *South Med J* 71(11):1345–1349
146. Fleischer ABJ, Clark AR, Rapp SR, Reboussin DM, Feldman SR (1997) Commercial tanning bed treatment is an effective psoriasis treatment: results from an uncontrolled clinical trial. *J Invest Dermatol* 109(2):170–174
147. Fortune DG, Richards HL, Kirby B, Bowcock S, Main CJ, Griffiths CE (2002) A cognitive-behavioural symptom management programme as an adjunct in psoriasis therapy. *Br J Dermatol* 146(3):458–465
148. Tausk F, Whitmore SE (1999) A pilot study of hypnosis in the treatment of patients with psoriasis. *Psychother Psychosom* 68(4):221–225
149. Nast A, Kopp I, Augustin M, Banditt KB, Boehncke WH, Follmann M, Friedrich M, Huber M, Kahl C, Klaus J, Koza J, Kreiselmaier I, Mohr J, Mrowietz U, Ockenfels HM, Orzechowski HD, Prinz J, Reich K, Rosenbach T, Rosumeck S, Schlaeger M, Schmid-Ott G, Sebastian M, Streit V, Weberschock T, Rzany B (2006) S3-Leitlinie zur Therapie der Psoriasis vulgaris. *JDDG Suppl* 2:S1–S126