Arch Dermatol Res (2012) 304:87–113
DOI 10.1007/s00403-012-1214-8

GUIDELINE

German S3-guidelines on the treatment of psoriasis vulgaris (short version)

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Received: 12 January 2012 / Accepted: 13 January 2012 / Published online: 17 February 2012

Abstract Psoriasis vulgaris is a common and often chronic inflammatory skin disease. The incidence of psoriasis in Western industrialized countries ranges from 1.5 to 2%. Patients afflicted with severe psoriasis vulgaris may experience a significant reduction in quality of life. 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 (Richards et al. in J Am Acad Dermatol 41(4):581–583, 1999). To optimize the treatment of psoriasis in Germany, the Deutsche Dermatologische Gesellschaft (DDG) and the Berufsverband Deutscher Dermatologen (BVDD) have initiated a project to develop evidence-based guidelines for the management of psoriasis first published in 2006 and now updated in 2011. The Guidelines focus on induction therapy in cases of mild, moderate, and severe plaque-type psoriasis in adults. This short version of the guidelines presents the resulting series

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of therapeutic recommendations, which were based on a systematic literature search and discussed and 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. in JDDG Suppl 2:S1–S104, 2011 or http://www.psoriasis-leitlinie.de).

Keywords Evidence-based guidelines · Psoriasis vulgaris · Treatment

Introduction

The Deutsche Dermatologische Gesellschaft and the Berufsverband Deutscher Dermatologen have initiated a project to develop evidence-based guidelines for the treatment of plaque psoriasis which were published in 2006 and now updated in 2011 [152, 155]. The full version has again been published in the Journal der Deutschen Dermatologischen Gesellschaft (JDDG 2011 Supplement 2 [152]) and is available at http://www.psoriasis-leitlinie.de. This article summarizes the key messages from the guidelines.

Background

Needs analysis/challenges in patient care

Psoriasis vulgaris is a common and almost always chronic skin disease

The prevalence of psoriasis in Western industrialized nations is 1.5–2% [157]. About 80% of psoriasis patients have the plaque form of disease. In Germany, the disease affects an estimated 1.6 million people. More than 90% have chronic disease [157].

Patients with plaque psoriasis have a substantially impaired quality of life

Studies on the impairment of quality of life in psoriasis patients have shown that, depending on the severity of disease, related disability or psychosocial stigmatization can present a considerable burden for the patient [198]. Patient surveys have found that the impact on quality of life is comparable to that experienced by patients with type 2 diabetes or chronic lung disease [183].

Patient satisfaction with current therapies is low and compliance is poor

Based on the results of patient surveys, only about one-fourth of patients report being very satisfied with the results of therapy; about 50% are moderately satisfied, and about one-fifth are not very satisfied [206]. There is also a high rate of medication non-compliance (up to 40%) [188]. Reasons for non-compliance include poor tolerability, fear, lacking information about potential side effects, low efficacy, and complicated usage [187, 242].

There is uncertainty concerning the use of systemic therapies

Nast et al. reported in a small survey of 39 dermatologists in private practice that, according to their own self-assessment, 76% of doctors surveyed had some uncertainty about prescribing systemic medications. 79% said they believed that this led to inadequate treatment with systemic therapies [153].

There is inadequate use of systemic therapy options in patients with moderate-to-severe psoriasis

Nast et al. reported in a study from 2006 with 54 dermatologists in private practice that in visits with 2,294 patients with moderate-to-severe psoriasis, about 50% of patients were treated with topical therapies alone. 17% received additional UV therapy and only about 30% were taking some form of systemic therapy [156].

The economic costs of disease are high

The costs of psoriasis, including the costs of statutory health care and other forms of insurance (e.g., unemployment coverage) as well as the costs for the patient himself (e.g., for basic therapies), are about 2,866 € per patient per year [19]. In 2002, about 20,000 patients with psoriasis vulgaris were hospitalized, primarily for initial treatment as well as for severe flare-ups. One German statutory health insurer (AOK West) reported that the number of disability cases for psoriasis vulgaris per year was 7.35 for men and 4.94 for women/10,000 insured persons (28 and 27 days) [216].

Goal of the guidelines

The overall goal of the guidelines is to provide dermatologists in private practice and clinicians with an accepted, evidence-based tool that can aid decision-making in the selection and implementation of appropriate and adequate therapies for patients with psoriasis vulgaris. The focus of

the guidelines is on induction therapy for mild to severe psoriasis vulgaris in adult men and women.

Improved patient care through implementation of guideline recommendations and optimization of physician knowledge of reported treatment efficacies

The personal experience of physicians and the use of traditional treatment concepts for psoriasis vulgaris should be augmented or even replaced by an evidence-based assessment of the anticipated results of a given therapy option based on medical science.

Assistance with optimal treatment implementation

The detailed description of systemic therapies, phototherapies, and photochemotherapy, including precise descriptions of their use and safety aspects, should help reduce any reservations on the part of doctors and patients with regard to certain therapies and ensure prompt, sufficient, and optimal treatment. The timely provision of information and prompt induction of adequate therapy should help prevent severe disease which frequently involves hospitalization and lost work days.

Improved patient awareness of current therapy options

A further version of the guidelines, designed for use by the patient, is currently being developed. The aim is to give patients an overview of possible therapies in terms of complications and optimal usage.

Enhancing compliance

Adequate patient compliance/adherence are often related to a good ratio between the benefits of therapy and the related effort, costs, and potential side effects. The choice of an effective therapy by the patient and doctor, taking into account the quality of life variables measured in recent studies, should help ensure a high treatment benefit. Providing information on the prevention and management of adverse effects should help limit or even prevent them. This in turn also increases compliance.

Quality of care indicators

Radtke et al. [180] have proposed eight indicators based on the Delphi method for measuring the quality of care of psoriasis patients. These quality indicators may be applied to the total population of psoriasis patients or used as indicators for monitoring changes in quality of care as a result of the guidelines: (1) average PASI in the total population; (2) average DLQI in the total population; (3) proportion of patients out of the total population with severe psoriasis vulgaris as measured by PASI (>20); (4) proportion of patients out of the total population who have severe psoriasis vulgaris as measured by DLQI (>10); (5) proportion of patients out of the total population who have previously received systemic therapy; (6) proportion of patients with severe psoriasis (PASI > 20) who report prior or current systemic therapy; (7) proportion of patients out of the total population who have been hospitalized in the last 5 years due to psoriasis; (8) average number of lost work days due to psoriasis among the total population.

Methods

A detailed description of the methods and procedures used for developing the guidelines may be found in the methods report (http://www.psoriasis-leitlinie.de). These guidelines are an update of the guidelines published in 2006 [154, 155].

Basis of data

A systematic literature search of published articles up to November 2009 was performed to evaluate the efficacy of various individual therapies. In addition to the 6,224 publications yielded by the literature search in the first version of the guidelines, we identified 1,443 new studies. Of these, 155 studies fulfilled the criteria for inclusion in the current guidelines and were included in the evaluations of treatment efficacy. The methodological quality of the chosen studies was determined using a "literature evaluation form" (LEF). Other aspects included in the guidelines were evaluated on the basis of information from the literature (without a systematic assessment) as well as on the basis of the personal experience of the guidelines expert committee. For 2006/2007, the results of the literature search for the EU guidelines were also included.

Evidence assessment

The efficacy of each intervention was systematically assessed using evidence-based criteria.

The methodological quality of each study was assessed using grades of evidence:

- A_1 Meta-analysis containing at least one randomized grade A_2 study. The results of the various studies included must be consistent.
- A_2 Randomized, double-blind, high-quality clinical comparative study (e.g., sample size calculation, flow chart, ITT analysis, sufficient sample size).
- B Randomized clinical study of lesser quality or other comparative study (non-randomized: cohort study or case–control study).

C Non-comparative study.

Evidence levels were also determined as part of evaluating the effectiveness of a drug given as monotherapy. This consisted of an evaluation of the overall evidence on the intervention:

1. Intervention is supported by grade A_1 studies or mostly consistent results from grade A_2 studies.
2. Intervention is supported by grade A_2 studies or grade B studies with mostly consistent results.
3. Intervention is supported by grade B studies or grade C studies with mostly consistent results.
4. Little or no systematic empirical evidence.

Passages requiring consensus
The authors of the guidelines have defined certain particularly relevant sections as requiring consensus. These passages were agreed on in consensus conferences and are highlighted in gray boxes.

Treatment recommendations

At present there is no clear step-by-step procedure or strict clinical algorithm for the treatment of psoriasis vulgaris. The criteria for selecting an appropriate therapy are complex. Certain aspects related to selecting a suitable treatment must be assessed and weighed individually. The decision for or against a therapy is made on an individual basis. The guidelines provide a scientifically based aid for decision-making and selection of an appropriate treatment. As such they constitute a medical tool for the optimal use of a necessary therapy.

Key recommendations formulated in the text are augmented by symbols representing the strength of the treatment recommendation. The following symbols have been used to help standardize the treatment recommendations:

↑↑	Measure is recommended	(strongly recommended)
↑	Measure may be recommended	(recommended)
→	Measure may be considered	(neutral recommendation)
↓	Measure cannot be recommended	(recommendation against its use)
↓↓	Measure should be avoided	(strongly disadvised)

Due to the focus of the guidelines on induction therapy, the recommendations in the update are limited to this phase. Some recommendations from the previous version are thus no longer included. This is in the interest of standardization and does not indicate any change to the recommendation level of a previously described drug.

The strength of recommendation takes into account various aspects concerning its effectiveness, including evidence level, safety aspects, feasibility, cost-to-benefit ratio, etc. The strength of the recommendations was agreed on in the framework of a consensus conference.

Results

Therapeutic strategies (Fig. 1)

Evaluation of topical and systemic therapies in tabular form

The following tables are intended to serve as a rough guide for evaluating therapy options. Cumulative calculations of individual aspects in the overall evaluation are not possible and cannot be used for a conclusive evaluation of a given therapy option. Each column should be viewed separately. The evaluation may vary significantly on a case-by-case basis. The varying degrees of severity of psoriasis render a direct comparison between systemic and topical therapies impossible. The evaluations are based on a literature review and expert opinion.

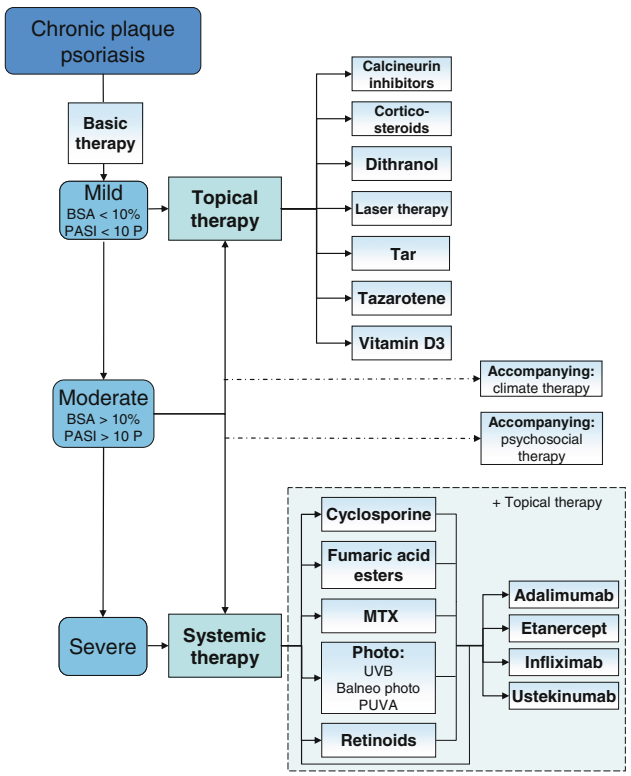


Fig. 1 Overview of therapy options under evaluation for use in chronic plaque psoriasis (the order of therapies is alphabetical and does not represent a ranking)

Topical monotherapy

Therapy	Efficacy	Evidence level	Safety/tolerability of induction therapy	Safety/tolerability for maintenance therapy	Feasibility (patient)	Feasibility (doctor)	Cost/ benefit
Calcineurin inhibitors	++	2/3	++	Not indicated	++	–[a]	++
Dithranol	+++	2	++	Not indicated	+[b] –[c]	+[b] –[c]	+++
Corticosteroids	++++[d]	1	+++	+	++	+++	+++
Coal tar	±	4	+	Not indicated	–	±	–
Tazarotene	++	2	++	++	±[e]	±[e]	++
Vitamin D3 derivatives	+++	1	+++	+++	+++	+++	++

Global assessment:

[a] No strong consensus (>75%) was achieved using the DELPHI method. The recommendation was therefore made based on a majority vote of 54% (guideline expert committee). Alternatively, members voted for "++." The reason for the discussion was "off-label" prescribing. The opinions on the effort involved diverged significantly

[b] Inpatient

[c] Outpatient

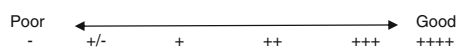
[d] At least class III steroids; also applies to fixed dose drug combinations

[e] No strong consensus (>75%) was achieved using the DELPHI method. The recommendation was therefore made based on a majority vote of 69% (guideline expert committee). Alternatively, members voted for "−." The reason for the discussion was the poor availability, i.e., available only via international pharmacies. The opinions on the effort involved diverged significantly

Phototherapy and systemic monotherapy

Therapy	Efficacy	Evidence Level	Safety/tolerability of induction therapy	Safety/tolerability of maintenance therapy	Feasibility (patient)	Feasibility (doctor)	Cost/ benefit[g]
Phototherapy							
UVB	+++	2	+++	Not indicated	±	+	++
PUVA	+++ to ++++	2	+[a] ++[b]	Not indicated	−	±	++
Adalimumab	+++	1	++	++	+++	++	+
Etanercept	+[d] +[e] ++[f]	1	++	++	+++	++	±
Cyclosporine	++ to +++	1	+	+	+++	++	++
Fumarate	++	2	+	+++	++	+++	+++
Infliximab	+++ to ++++	1	+	++	+++	±	+
Methotrexate	+ to ++	2	+	++	++	++	+++
Retinoids[c] (systemic)	+	2	+	+	+	++	±
Ustekinumab	+++	1	++	++	+++	++	+

Global assessment:



[a] Systemic PUVA

[b] Bath/cream PUVA

[c] Retinoid therapy is generally not advised for women of childbearing age

[d] For 1 × 25 mg

[e] For 1 × 50 mg

[f] For 2 × 50 mg

[g] For a 12-week regimen of induction therapy

(a) *Efficacy* The value in the column "efficacy" reflects the percentage of patients who achieved a reduction in PASI score >75%.

Scale	Systemic therapy (%)	Topical therapy (%)
++++	ca. 90	ca. 60
+++	ca. 70	ca. 45
++	ca. 50	ca. 30
+	ca. 30	ca. 15
±	ca. 10	ca. 5
–	not defined	not defined

The evidence level applies to demonstrated efficacy.

(b) *Safety/tolerability of induction/maintenance therapy* The risk of severe side effects or the likelihood of side effects resulting in discontinuation of therapy.

(c) *Feasibility (patient)* Evaluated factors include the amount of time involved in using the therapy, its actual usage, and ease of administration.

(d) *Feasibility* (*doctor*) Factors that are evaluated include the amount of work involved (documentation, educating the patient, monitoring), requirements for equipment and personnel, time involved for doctor/patient interactions, reimbursement of treatment measures, invoicing problems/risk of recourse claims by insurers.

(e) *Cost/benefit* This is assessed according to the costs of induction or maintenance therapy.

The assessment of safety/tolerability for induction or maintenance therapy, as well as the feasibility of therapy for the doctor and patient, and costs/benefits are measured on a scale of − (poor) to ++++ (good). Grades are based on information from a literature review and expert opinion. No evidence level is cited since it was not specifically included in the literature search.

Evaluation of topical therapies

Calcineurin inhibitors

Table 1 Summary table

Calcineurin inhibitors	
Approval in Germany	
Pimecrolimus	2002 (atopic dermatitis, not approved for use in psoriasis vulgaris)
Tacrolimus	2002 (atopic dermatitis, not approved for use in psoriasis vulgaris)
Recommended initial dosage	Protopic® for use on the face: begin with 0.03% ointment, later increase dosage to 0.1% ointment Elidel® cream: 1–2 ×/daily
Recommended maintenance dosage	Individual treatment modification
Onset of clinical effect	After about 2 weeks
Response rate	40–50% of patients have significant improvement or complete clearance after 6–12 weeks (evidence level: 2)
Main contraindications	Contraindicated in pregnant or nursing women due to lack of data
Important UAEs	Burning of the skin, increased rate of skin infections
Important drug interactions	No known drug interactions
Misc.	Important note: do not combine with phototherapy

Summary evaluation

Out of eight studies on topical calcineurin inhibitors (pimecrolimus, tacrolimus), four met the inclusion criteria of the guidelines. [131,35,163,140] These studies reported a significant improvement or complete clearance of lesions in 40 - 50 % of patients after six to twelve weeks (EL 2).

Topical calcineurin inhibitors may be used in psoriasis patients for the treatment of areas that are sensitive to steroids, especially the face, flexures, and anogenital region.

Undesirable adverse effects such as burning and irritation can occur. The feasibility for the patient is good, but it is limited for the physician due to off-label use of the drug.

Since calcineurin inhibitors are not approved for the treatment of psoriasis vulgaris, off-label-use is the only available option at this time.

Treatment recommendation

Topical application of tacrolimus or pimecrolimus 1 - 2 x/daily may be considered for the treatment of psoriasis vulgaris involving certain areas such as the face, intertriginous regions, and anogenital region. ➔

Their use on other areas of the body is not advised, given other alternatives, as the data are insufficient and there is lacking approval for their use in psoriasis. ➔

Coal tar

Table 2 Summary table

Coal tar	
Approval in Germany	Listed since 2000 [German Drug Codex (DAC) code: S-170], historical use, various tar-based topical therapies are approved, tar used as an anti-psoriasis drug after 1925 following publication by Goeckermann
Recommended control parameters	Long-term use/large areas of the skin: possible clinical controls of potential development of carcinoma of the skin
Recommended initial dosage	5–20% ointment or gels for local therapy, 1 ×/daily for a few hours
Recommended maintenance dosage	Not suitable for long-term use (max. 4 weeks, DAC 2000)

Table 2 continued

Coal tar	
Onset of clinical effect	After 4–8 weeks, combination use with UV therapy increases effectiveness
Response rate	Insufficient data for assessing response rate to monotherapy (EL 4)
Main contraindications	Pregnancy and nursing
Important UAEs	Color, odor, carcinogenic risk, phototoxicity which is part of the desirable effect
Important drug interactions	No known interactions with external use
Misc.	DAC 2000 (DAC code: S-170), hazardous materials appendix 4, no. 13

Summary evaluation

Of the 21 studies that were evaluated, six met the criteria for inclusion in the guidelines. [16,52,130,69,13,8]
Given that there is only one monotherapy (grade C) study available, it is impossible to make any conclusive statements on the efficacy of coat tar monotherapy (EL 4).
Clinical studies on coal tar with phototherapy have reported mixed results. Studies report that after 15 - 20 treatments with UV therapy, 45 - 80 % of patients achieve at least PASI 75. The additive effect of coal tar, compared with UV therapy alone, has not been sufficiently proven, however.
The acceptance of coal tar preparations is low due to their color and odor. Given the availability of more effective, lower-risk, and more practical treatment alternatives, the use of coal tar monotherapy for the treatment of plaque psoriasis is largely outdated.
Only after careful consideration of the therapeutic benefit, and after considering lower-risk therapy alternatives, may coal tar perhaps be used in combination with UVB for the treatment of refractory plaque psoriasis.

Treatment recommendation

Coal tar monotherapy is not recommended for the treatment of psoriasis vulgaris.	↓↓
Under exceptional circumstances, the use of a coal tar preparation in combination with UV therapy may be considered in individual patients for the treatment of psoriasis.	→

Corticosteroids

Table 3 Summary table

Steroids	
Approval in Germany	1956 (psoriasis vulgaris)
Recommended control parameters	None
Recommended initial dosage	1–2 ×/daily
Recommended maintenance dosage	Taper after drug takes effect
Onset of clinical effect	After 1–2 weeks
Response rate	For, e.g., beta methasone dipropionate 2 ×/daily marked improvement or complete clearance in 46–56% of patients after 4 weeks (EL 1)
Main contraindications	Bacterial, viral skin diseases

Table 3 continued

Steroids	
Important UAEs	Folliculitis, perioral dermatitis, skin atrophy
Important drug interactions	None
Misc.	–

Summary evaluation

Out of 122 studies, 36 met the criteria for inclusion in the guidelines. [205,79,50,122,100,20,42,173,202,208,236,60,164,124,134,103,113,12,95,142,229,123,53,194,112,237,144,192,104,166,37,99,58,30,209,210]
Significant improvement or complete clearance was found in 25 - 77.8 % of patients who used betamethasone dipropionate (EL 1).
Among patients who were given mometasone there was > 75 % improvement in lesions in 36.3 - 64 % (EL 1)
Most studies on class IV steroids (clobetasol 17-propionate 2 x/daily) reported PASI 75 in 68 - 89 % of patients (EL 1).
The effectiveness of topical steroids may be enhanced by additive use of salicylic acid (EL 1).
The combination with other systemic or topical therapies also leads to improved remission rates. Common combinations include topical vitamin D_3 derivatives.
No serious adverse effects have been reported during induction therapy. Long-term use steroids can cause various typical side effects such as skin atrophy and telangiectasias.
Feasibility is good for the patient and doctor.

Treatment recommendation

Induction therapy with class III topical steroids is recommended for patients with mild to moderate psoriasis vulgaris.	↑↑
Induction therapy with class IV topical steroids may be recommended for patients with mild to moderate psoriasis vulgaris after carefully considering the increased efficacy and theoretically increased risk of adverse effects.	↑

Dithranol

Table 4 Summary table

Dithranol	
Approval in Germany	
Psoralon®	1983 (psoriasis vulgaris)
Psoradexan®	1994 (psoriasis vulgaris)
Micanol®	1997 (psoriasis vulgaris)
Recommended control parameters	Intensity of skin irritation
Recommended initial dosage	Start with 0.5% preparation for long-term therapy or 1% for short-contact therapy, increase if tolerated
Recommended maintenance dosage	Not recommended for long-term therapy
Onset of clinical effect	After 2–3 weeks
Response rate	Significant improvement or complete clearance in 30–70% of patients (EL 2)
Main contraindications	Acute, erythrodermic psoriasis, pustular psoriasis
Important UAEs	Burning and redness of the skin in >10%
Important drug interactions	–
Misc.	–

Summary evaluation

Out of 67 evaluated studies, 11 studies on dithranol monotherapy met the criteria for inclusion in the guidelines. [148,4,49,98,136,178,179,209,214,225,3]
The results of these studies show total remission (PASI reduction of 100 %) in 30 to 70 % and partial remission (PASI reduction of 75 %) in 26 to 100 % of patients after five to eight weeks (EL 2). Drug efficacy may be increased by combining it with calcipotriol-based creams or UVB phototherapy.
Therapy should be conducted for four to eight weeks. Maintenance or long-term therapies are not feasible with dithranol and do not offer any benefit.
The safety of the drug is very good. Burning, redness and transitory brown discoloration are the only adverse effects reported. There are no reports of adverse systemic effects.
Feasibility is limited for outpatient use. Its use is feasible in hospitalized patients, and there is a good cost-to-benefit ratio.
For the treatment of severe psoriasis vulgaris, combination use with phototherapy or other topical preparations (calcipotriol) may enhance the treatment response and is thus recommended.

Treatment recommendation

Dithranol monotherapy may be recommended for induction therapy in hospitalized patients with mild to moderate plaque psoriasis. ↑

Monotherapy may be considered for outpatient induction therapy in patients with mild or moderate plaque psoriasis. →

Tazarotene

Table 5 Summary table

Tazarotene	
Approval in Germany	1997 (psoriasis vulgaris)
Recommended control parameters	Check for development of skin irritation
Recommended initial dose	Start with 1 ×/daily (evenings) tazarotene gel 0.1% for ca. 1–2 weeks
Recommended maintenance dose	Tazarotene gel 0.1% 1 ×/daily
Onset of clinical effect	After 1–2 weeks
Response rate	After 12 weeks of tazarotene gel 0.1% roughly half of patients show at least 50% improvement (EL 2)
Main contraindications	Pregnant and nursing women
Important UAEs	Pruritus, burning, erythema, irritation
Important drug interactions	Avoid simultaneous use of preparations with irritative and strong drying effects
Misc.	Tazarotene is approved for use in Germany, but is no longer sold and is currently available only as a 0.1% formulation through international pharmacies

Summary evaluation

Seven of the 12 studies evaluated met the criteria for inclusion in the guidelines. [235,74,115,121,81,177,232]
After about 12 weeks of treatment with tazarotene 0.1 % 1 x/daily about 50 % of patients achieve at least a 50 % improvement in skin lesions (EL 2).
Combination therapy with topical steroids can help optimize treatment success and reduce commonly reported skin irritation (EL 2).
There are no reports of serious side effects related to the drug. Contact with healthy skin should be avoided to prevent irritation.
Tazarotene is approved for use in Germany, but is no longer on the market. The drug may be ordered through an international pharmacy. This limits the feasibility of its use.

Treatment recommendation

Topical use of tazarotene may be considered in the treatment of mild to moderate psoriasis vulgaris. →

Vitamin D3 and vitamin D3 analogues

Table 6 Summary table

Vitamin D_3 and analogues	
Approval in Germany	
Calcipotriol	1992 (psoriasis vulgaris)
Tacalcitol	1994 (psoriasis vulgaris)
Calcitriol	1999 (psoriasis vulgaris)
Calcipotriol/ betamethasone	2002 (psoriasis vulgaris)
Recommended control parameters	Check for development of skin irritation
Recommended initial dosage	Calcipotriol: 1–2 ×/daily on affected areas of the skin, maximum 30% of BSA
	Tacalcitol: 1 ×/daily on affected areas of the skin, maximum 20% of BSA
	Calcitriol: 2 ×/daily on affected areas of the skin, maximum 35% of BSA
Recommended maintenance dosage	Calcipotriol: 1–2 ×/daily, up to 100 g/ weekly up to 1 year
	Tacalcitol: 1 ×/daily for 8 weeks to 18 months maximum 15% of BSA with up to 3.5 g/daily
	Calcitriol: lacking experience with use for longer than 6 weeks
Onset of clinical effect	After 1–2 weeks
Response rate	30–50% patients experience significant improvement or complete clearance after 4–6 weeks (EL 1)
Main contraindications	Disorders with altered calcium metabolism, severe liver and kidney disease
Important UAEs	Skin irritation (redness, itching, burning)
Important drug interactions	Drugs that elevate calcium levels (e.g., thiazide diuretics), avoid concomitant use of topical salicylic acid (inactivation)
Misc.	–

Summary evaluation

Out of 68 evaluated studies, 27 met the criteria for inclusion in the guidelines. [116,243,84,118,123,112,37,194,144,30,53,104,192,162,166,237,85,98,223,225,131,163,58,22,181,1,2]
The majority of data are on calcipotriol. For treatment of mild to moderate psoriasis, 30 - 50 % of patients treated with calcipotriol achieve significant improvement or complete clearance within a few weeks (EL 1).
The efficacy of calcitriol and calcipotriol appears comparable based on available studies (EL 1).
The efficacy and tolerability of vitamin D_3 derivatives can be further enhanced by combining them with topical steroids (EL 1).
There are only a few clinical studies available on the use of tacalcitol (EL 3).
Topical use of vitamin D_3 derivatives (tacalcitol) has been shown to have synergistic effects with systemic cyclosporine in the treatment of severe psoriasis (EL 3).
Local therapy with vitamin D_3 derivatives is generally well tolerated by the patient and feasible for doctors and patients. Use may be limited by potential transitory skin irritation, especially in treatment of the face or intertriginous zones.

Treatment recommendation

Vitamin D_3 derivatives are recommended for use in induction therapy for mild to moderate psoriasis. ↑↑

Combination therapy with vitamin D_3 derivatives and steroids is recommended in the first four weeks as induction therapy for mild to moderate psoriasis. ↑↑

Phototherapy

Table 7 Summary table

Phototherapy	
Approval in Germany	Clinical experience >50 years depending on modality
Recommended control parameters	Regular inspection of the skin (especially for dermatitis solaris)
Recommended initial dosage	Individual dosage based on skin type, alternatively:
	UVB: 70% of minimal erythema dose (MED)
	Oral PUVA: 75% of minimal phototoxic dose (MPD)
	Bath/cream PUVA: 20–30% minimal phototoxic dose (MPD)
Recommended maintenance dosage	Increase depending on erythema
Onset of clinical effect	After 1–2 weeks
Response rate	UVB: 50–75% of patients achieve PASI 75 after 4–6 weeks (EL 2)
	PUVA: 75–100% of patients achieve PASI 75 after 4–6 weeks (EL 2)
Main contraindications	Photodermatoses/photosensitivity, skin cancer, immunosuppression
	Only PUVA: pregnant or nursing women
Important UAEs	Erythema, itching, blistering, malignancy
	Only oral PUVA: nausea
Important drug interactions	Important note: photosensitizing drug
Misc.	Combination with topical preparations has synergistic effects; phototherapy should not be combined with cyclosporine A

Instructions for application

Pre-treatment procedures

- The treating physician should conduct a thorough inspection of the entire body surface, especially for signs of cancerous lesions, precancerous lesions, and dysplastic nevus cell nevi.
- The patient should be informed about the course of therapy, possible side effects, and potential long-term risks – in particular the increased risk of cancer as a result of therapy. He or she should be made aware of synergistic effects resulting from additional UV exposure during leisure time or self-treatment.
- Before beginning oral PUVA therapy, the patient should be examined by an ophthalmologist. Protective goggles should also be obtained.

Measures during therapy

- The UV dose must be precisely recorded (J/cm^2 or mJ/cm^2).
  Erythema development must be controlled regularly before increasing the dosage.
- Regular monitoring of therapy also includes documentation of the success of therapy, side effects, and any concomitant therapy use.
- Protective goggles should be worn during UV lig ht therapy.
- Unless they are the focus of therapy, chronic sun exposed areas (face, neck, backs of the hands) and genital regions should be protected from exposure to UV light.
- Adequate protective measures against exposure to sunlight are necessary during therapy.

Post-therapy measures

- After completing a treatment series, the cumulative UV dosage and the number of treatment sessions must be recorded and given to the patient.
- Patients with a high cumulative UV dose should undergo lifelong regular skin cancer screening.

Summary evaluation

For monotherapy, 35 studies on UV phototherapy [64,47,125,139,240,201,161,34, 67,172,11,109,129,141,54,175,189,181,16,130,52,69,8,13,114,135,106,133,72,48, 23,24,174,88,197], 38 on PUVA therapy [27,76,83,138,171,204,197,7,238,10,220, 200,105,101,18,25,28,52,107,108,169,92,190,14,44,45,29,195,170,68,215,89,218, 26,191,228,233,221], and 10 studies on laser therapy [87,102,217,61,96,99,58,72, 48,211] met the inclusion criteria of the guidelines.
50 - 75 % of patients treated with UVB phototherapy achieved at least a 75 % improvement in PASI score after four to six weeks and often there was complete clearance of lesions (EL 2).
Some 75 - 100 % of all patients treated with PUVA therapy achieve at least a 75 % improvement in PASI score after four to six weeks, and complete clearance of lesions is common (EL 2).
Dermatitis solaris, as a result of overdose, is by far the most commonly reported adverse effect, and is also frequently reported. For repeated or long-term therapy, the consequences of high cumulative UV dosages, such as premature aging of the skin, must be taken into account. There is also a risk of developing cancer which has been shown for oral PUVA and is considered likely for local PUVA and UVB.
The feasibility of therapy for the doctor is considerably limited by the need for space, financial considerations, and personnel/time. For the patient, feasibility it is significantly limited by the amount of time involved.
The cost-to-benefit ratio for phototherapy is good from the perspective of health insurers. Yet the cost and time involved for the patient are potentially considerable.

Treatment recommendation

UVB and PUVA are recommended for induction therapy for moderate to severe psoriasis vulgaris, especially if there is involvement of a large body surface area.	↑↑
Despite the superior efficacy of PUVA compared with UVB therapy alone, narrow band UVB therapy may be considered as the first choice for phototherapy. Feasibility is better and there is a lower risk of malignancy.	↑
The use of excimer laser may be recommended for targeted therapy of individual psoriatic plaques.	↑
The combination with topical vitamin D_3 derivatives may be recommended for improving the response rate.	↑
The customary combination with dithranol and steroids may be recommended based on clinical experience, but not on the basis of the available data.	↑
Given low feasibility and an association with long-term adverse effects due to the cumulative UV dose, long-term phototherapy is not advisable.	↓

Evaluation of systemic therapies

Adalimumab

Table 8 Summary table

Adalimumab	
Approval in Germany	2005 (psoriatic arthritis)
	2007 (plaque psoriasis)
Recommended control parameters	Exclude tuberculosis before treatment initiation; during therapy: blood count, liver values, clinical signs of infection
Recommended initial dosage	80 mg subcutaneously
Recommended maintenance dosage	40 mg subcutaneously every 2 weeks
Onset of clinical effect	Four to eight weeks; maximum efficacy at 16 weeks
Response rate	PASI 75 achieved in 71–80% of patients with moderate to severe psoriasis (EL 1)
Main contraindications	Chronic infections, tuberculosis, cardiac insufficiency (NYHA class III/IV)

Table 8 continued

Adalimumab	
Important UAEs	Reactions at the injection site, serious infections, hair loss, autoimmune phenomena
Important drug interactions	Anakinra, abatacept
Misc.	–

Instructions for application

Pre-treatment procedures
- Rule out acute infection
- Definitive exclusion of tuberculosis as per current recommendations of the Paul Ehrlich Institute [51], see Appendix 1
- If warranted by patient history or clinical or laboratory chemical tests, HIV and viral hepatitis should be excluded.
- Contraception must be ensured and pregnancy ruled out in women of child-bearing age
- Patients should be informed that serious infections have occurred with use of the drug and that prompt medical attention is required if infection is suspected.

Measures during therapy
- Surveillance for infection; if there is suspected infection, therapy should be discontinued, at least temporarily.

Post-therapy measures
- None

Table 9 Monitoring

Months → Diagnosis ↓	Before	1	3	Every 2 - 3 months
Blood differential	X	X	X	X
ASAT, ALAT, γGT	X	X	X	X
Pregnancy test (urine)	X			
For suspected infection, see pre-treatment procedures				

Summary evaluation

Seven of the nine evaluated studies met the criteria for inclusion in the guidelines. [75,146,165,186,196,226,21,231]
This includes two studies from the research conducted for the European S3 psoriasis guideline. Some 71 - 80 % of patients with moderate to severe psoriasis who are treated with adalimumab (initial dose of 80 mg given subcutaneously, followed by 40 mg every other week) achieve at least PASI 75 after 12-16 weeks (EL 1).
During the induction phase, adalimumab is one of the most highly effective medications for the treatment of psoriasis vulgaris. Adalimumab is suitable for long-term therapy.
In patients with concomitant psoriatic arthritis, administration of TNF-α antagonists is especially useful. Various saf ety aspects related to the use of should be recalled. Foremost among these is the risk of serious infection. This requires careful assessment of the indications for therapy, as well as education and monitoring of the patient.
Given the vast numbers of patients who have been treated with adalimumab (including for diseases other than psoriasis), the risk of adverse effects is readily evaluated.
Therapy is feasible for the doctor and patient. Combination therapy with MTX and adalimumab could also counteract the formation of antibodies to the drug, as has been seen with the use of MTX and infliximab.

Treatment recommendation

Adalimumab is recommended for induction therapy in patients with moderate to severe plaque psoriasis, especially if other forms of therapy have failed, are not tolerated, or are contraindicated. ↑↑

Cyclosporine

Table 10 Summary table

Cyclosporine	
Approval in Germany	1983 (transplantation medicine) 1993 (psoriasis vulgaris)
Recommended control parameters	See below
Recommended initial dosage	2.5–3 (max. 5) mg/kg body weight
Recommended maintenance dosage	Interval therapy (8–16 weeks) with a dosage reduction at the end of induction therapy (e.g., 0.5 mg/kg body weight every 14 days) or Continuous long-term therapy with dosage reduction, e.g., 50 mg every 4 weeks after week 12 and increasing the dosage by 50 mg if relapse occurs Maximum 2 years treatment duration
Onset of clinical effect	After about 4 weeks
Response rate	Dose-dependent, after 8–16 weeks at 3 mg/kg body weight, PASI 75 in 50–70% (EL 1)
Main contraindications (limited selection)	Absolute contraindications: Relevant kidney dysfunction Uncontrolled arterial hypertension Uncontrolled infection Relevant malignancy (current or past, especially hematological diseases and cutaneous malignancies with the exception of basal cell carcinoma) Relative contraindications: Relevant liver dysfunction Pregnancy and lactation Concomitant use of substances that interact with cyclosporine Simultaneous light therapy or PUVA pre-therapy with a cumulative dose >1,000 J/cm^2 Concomitant use of other immunosuppressants, retinoids, or long-term pre-therapy with MTX
Important UAEs	Renal dysfunction, increased blood pressure, liver dysfunction, nausea, loss of appetite, vomiting, diarrhea, hypertrichosis, gingival hyperplasia, tremors, fatigue, paresthesia

Table 10 continued

Cyclosporine	
Important drug interactions (limited selection)	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
	Decrease of the cyclosporine level (CYP3A induction) through:
	Carbamazepine, phenytoin, barbiturates, metamizole, St. John's wort
	Possible reinforcement of nephrotoxic adverse drug reactions through:
	Aminoglycosides, amphotericin B, ciprofloxacin, acyclovir, non-steroidal antiphlogistics
	Specific interactions:
	Potassium-saving substances: increased risk of hyperpotassämia
	Reduced clearance of:
	Digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (e.g. lovastatin), diclofenac
Misc.	In transplant patients, increased risk of lymphoproliferative diseases
	In psoriasis patients excessive light therapy can lead to increased risk of squamous cell cancer
	Only moderately effective against psoriatic arthritis and not approved
	Also been used successfully in children with chronic inflammatory diseases

Instructions for application

Pre-treatment procedures

General measures

- Patient history including past and current diseases (e.g., severe infections, malignancy, kidney or liver diseases), accompanying medication (see drug interactions in long version [152]).

Specific measures

- With corresponding patient history or clinical or laboratory signs, HIV infection and viral hepatitis should be excluded.
- Inspection for potentially malignant skin lesions.
- Signs of existing infection
- Take blood pressure measurements at two different times.

Patient education:

- Patients should be made aware that any infection may be more severe or have a typical symptoms and course and they must therefore seek prompt medical attention.
- Drug interactions (also inform other treating physicians of therapy)
- Ensure contraception and rule out pregnancy in women of childbearing age (important note: diminished efficacy of progesterone-based contraceptive drugs)
- Avoid excessive exposure to sunlight, use of sun protection

Measures during therapy

Interview / examination

- Status of skin and mucous membranes (e.g., increased body hair, swollen gums, rule out skin cancer)
- Signs of existing infection
- Gastrointestinal symptoms and neurological symptoms
- Repeat recommendation to protect against exposure to sunlight
- Check co-medication
- Measure blood pressure
- In uncomplicated low-dose long-term therapy (2.5 -3mg/kg body weight daily) later 2-month control intervals maybe used
- Shorter intervals, e.g., in patients with risk factors, whenincreasing dosage, with the use of metabolic drugs or drugs with potential interactions
- Creatinine clearance if the creatinine plasma levels appear abnormal
- In certain patients undergoing intermittent orshort-term therapy, a smaller number of controls (e.g., regular control of blood pressure and creatinine values) may be sufficient
- Assessment of cyclosporine levels may occasionally be wise especially with suspected non-compliance or toxicity due to drug interactions

Post-therapy measures

- None

Table 11 Monitoring

Weeks → Diagnosis ↓	Before	2	4	8	12	16
Blood count[a]	X	X	X	X	X	X
Liver values[b]	X	X	X	X	X	X
Electrolytes[c]	X	X	X	X	X	X
Serum creatinine	X	X	X	X	X	X
Uric acid	X		X	X	X	X
Pregnancy test (urine)	X					
Cholesterol, triglycerides[d]	X		X		X	
Magnesium[e]	X		X		X	

[a] Erythrocytes, leukocytes, thrombocytes + blood differential
[b] Transaminase , γGT, bilirubin
[c] Sodium, potassium
[d] Assess twice if possible (empty stomach) and additionally at week -2 and week 0
[e] Only if indicated (e.g., muscle cramps)

Summary evaluation

Of the studies evaluated on cyclosporine therapy in psoriasis patients, 28 meet the criteria for inclusion in the guidelines. [56,113,55,57,119,62,94,143,213,39,239, 207,91,120,71,160,63,93,65,129,137,185,176,230,67,82,1,2] This includes 15 studies from the research for the European S3 psoriasis guidelines.
After 12-16 weeks, 50 - 70 % patients achieve PASI 75 (EL 1).
Cyclosporine is especially suitable for induction therapy.
In long-term therapy, after one to two years maximum, continuation of therapy should be carefully considered given potential side effects, especially nephrotoxicity and increased blood pressure as well as the increased risk of cancer.
Given the large number of patients who have been treated with cyclosporine (for other diseases as well), the risk of undesirable adverse effects is predictable.
Various drug interactions can occur with the use of cyclosporine, on the one hand leading to altered availability of cyclosporine or the concomitant drug and on the other hand increasing the risk of adverse effects.
Combination use with topical preparations is helpful in the treatment of plaque psoriasis, especially since it appears that concomitant local therapy with vitamin D_3 analogues or steroids can help reduce cyclosporine dosage without diminishing its effectiveness.

Treatment recommendation

Cyclosporine may be recommended, especially for induction therapy, in patients with moderate to severe psoriasis vulgaris. ↑

Combination therapy with cyclosporine and topical preparations in the treatment of psoriasis vulgaris may be recommended. ↑

Etanercept

Table 12 Summary table

Etanercept	
Approval in Germany	2002 (psoriatic arthritis)/2004 (psoriasis vulgaris)/2008 (psoriasis vulgaris in children)
Recommended control parameters	Blood count, liver values
Recommended initial dosage	2 × 25, 1 × 50 or 2 × 50 mg/weekly
Recommended maintenance dosage	2 × 25 mg/weekly, 1 × 50 mg/weekly
Onset of clinical effect	After 6–12 weeks; maximum efficacy after 24 weeks
Response rate	PASI 75 in 34% (2 × 25 mg), 38% (1 × 50 mg) and 49% (2 × 50 mg) after 12 weeks (EL 1)
Main contraindications	Infections, pregnancy, nursing
Important UAEs	Local reaction, infections
Important drug interactions	Anakinra (IL-1 receptor antagonist), abatacept (co-stimulation inhibitor
Misc.	–

Instructions for application

Pre-treatment procedures

General measures

- Rule out acute infection
- Exclude TB based on current recommendations by the Paul Ehrlich Institute [51], see Appendix 1
- Ifwarranted by the patient history or the results of clinical or laboratory tests, rule out HIV infection and viral hepatitis.

Specific measures

- Patients must ensure adequatecontraception / rule out pregnancy in women of childbearing age
- Patients should be informed of the potential for severe and atypicalinfections and should seek promptmedical attention if symptoms occur.

Measures during therapy

- Monitoring for infections; if an infection is detected or suspected, stoptherapy at least temporarily
- Discontinue therapy if pregnancy occurs

Post-therapy measures

- None

Table 13 Monitoring

Months → Diagnosis ↓	Before	1	3	6	8
Blood differential	X	X	X	X	X
ALAT, ASAT, γGT	X	X	X	X	X
Pregnancy test (urine)	X				
If there is suspicion of infection, see pre-treatment procedures.					

Summary evaluation

Out of 20 studies assessed in regard to the efficacy of etanercept monotherapy in patients with psoriasis, 16 met the criteria for inclusion. [80,128,46,168,227,219,36,149,70,109,110,241,224,17,32,31] This includes eight studies from the research for the European S3 psoriasis guideline.
In treatment with etanercept 2 x 25 mg or 1 x 50 mg given subcutaneously once a week, about 35 % or 38 % of patients achieve PASI 75 after 12 weeks. For therapy with 2 x 50 mg given subcutaneously every week for 12 weeks, about 50 % of patients achieve PASI 75 (EL 1). The maximum efficacy of etanercept is not reached until after the induction phase. Etanercept is suitable for long-term use. Based on the data from available studies, an increase in effectiveness in long-term therapy of psoriasis vulgaris may be expected in some patients.
The use of TNF-α antagonists is especially beneficial for patients with psoriatic arthritis. The efficacy and safety of etanercept are not influenced by the formation of antibodies to the drug. Various safety aspects should be considered when administering etanercept. One of the most important is the risk of infection. Careful evaluation of the indications for use of the drug as well as education and monitoring of the patient are essential.
Given the widespread use of etanercept (for other diseases as well), the risk of side effects related to its use is readily assessed.
Therapy is feasible for the doctor and patient.
Combination use of etanercept with MTX or acitretin can have synergistic effects.

Treatment recommendations

Etanercept 2x50 mg is recommended for induction therapy in patients with moderate to severe psoriasis vulgaris, especially if other treatment forms have been unsuccessful, are not tolerated, or are contraindicated. ↑↑

Etanercept 1 x 50 mg or 2 x 25 mg may be recommended for induction therapy. ↑

Comment: In the framework of the consensus conference, there was no strong consensus (>75 %) on the therapy recommendations for etanercept. The recommendation was based on a majority vote of 62 % of the guidelines experts.
Alternative formulations were "may be recommended" (2 x 50 mg) or "may be considered" (1 x 50 or 2 x 25). This was due to the initially comparatively lower efficacy of etanercept versus other biological agents, given that etanercept reaches maximum efficacy only after the induction phase.

Fumaric acid esters

Table 14 Summary table

Fumaric acid esters	
Approval in Germany	1995 (psoriasis vulgaris, moderate to severe disease)
Recommended control parameters	Serum creatinine, transaminase/γGT, blood differential, urine status
Recommended initial dosage	Based on recommended dosage scheme
Recommended maintenance dosage	Individual dosage modification
Onset of clinical effect	After about 6 weeks
Response rate	PASI 75 in 50–70% of patients at the end of the induction phase after 16 weeks (EL 2)
Main contraindications	Chronic diseases of the gastrointestinal tract and/or kidneys as well as chronic diseases that are associated with diminished leukocyte count or function
	Patients with malignant diseases
	Pregnant or nursing women
Important UAEs	Gastrointestinal complaints, flush, lymphopenia, eosinophilia
Important drug interactions	No known drug interactions
Misc.	–

Table 15 Dosing scheme 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 procedures

– Laboratory controls see Table 16

Measures during therapy

– Laboratory controls see Table 16

Post-therapy measures

– None

Table 16 Monitoring

Weeks → Diagnosis ↓	Before	Up to 4th month every 4 weeks	After 4th month every 8 weeks
Blood differential[a]	X	X	X
Liver values[b]	X	X	X
Serum creatinine	X	X	X
Urine status	X	X	X

[a] Erythrocytes, leukocytes, thrombocytes, blood differential

[b] Transaminase, γGT

Summary evaluation

Out of 13 evaluated studies, nine met the criteria for inclusion in the guidelines. [6,111,158,5,15,33,132,151,73] After 16 weeks, 50 - 70 % of patients achieved PASI 75 (EL 2).
Fumaric acid esters are suitable for long-term therapy.
The clinical experience with fumaric acid esters is much greater than the documentation of efficacy and safety of their use in clinical studies.
Clinical use of the drug is limited by gastrointestinal effects and symptoms of flush.
The feasibility for the doctor and patient is good.
An advantage of fumaric acid esters is their low rate of drug interactions.

Treatment recommendation

Fumaric acid esters may be recommended for induction therapy in adult patients with moderate to severe psoriasis vulgaris. ↑

Infliximab

Table 17 Summary table

Infliximab	
Approval in Germany	2004 (psoriatic arthritis)/2005 (psoriasis vulgaris)
Recommended control parameters	Before therapy rule out tuberculosis, during therapy: leukocyte and thrombocyte counts, liver values, clinical signs of infection
Recommended initial dosage	5 mg/kg of body weight
Recommended maintenance dosage	5 mg/kg of body weight (initially: infusions on day zero, week two and week six; maintenance therapy: every 8 weeks)
Onset of clinical effect	After 1–2 weeks
Response rate	PASI 75 in ≥80% in patients with moderate to severe psoriasis vulgaris (EL 1)
Main contraindications	Acute or chronic infections, tuberculosis, cardiac insufficiency NYHA III–IV
Important UAEs	Infusion reactions, severe infections, autoimmune phenomena
Important drug interactions	Anakinra
Misc.	–

Instructions for application

Pre-treatment procedures

- Exclude acute infection
- Certain exclusion of tuberculosis based on current recommendations of the Paul Ehrlich Institute [51], see Appendix 1
- If warranted by the patient history or clinical or laboratory chemical signs, rule out HIV infection or viral hepatitis.
- Reliable contraception / rule out pregnancy in women of childbearing age
- Patients should be informed of the potential for sever e and atypical infections and should seek prompt medical attention if symptoms occur.

Measures during therapy

- Monitoring of the patient up to one hour after infusion
- Monitoring of the patient for infections; if infection is suspected, treatment should be interrupted

Post-therapy measures

- None

Table 18 Monitoring

Months → Diagnosis ↓	Before	1	2	3
Blood differential	X	Before each additional infusion		
ASAT, ALAT, γGT	X	Before each additional infusion		
Pregnancy test (urine)	X			
For suspected infections, see pre-treatment procedures				

Summary evaluation

Out of 15 evaluated studies, nine studies on monotherapy met the criteria for inclusion in the guidelines. [9,78,184,203,145,40,199,126,38] This includes six studies from the research for the European S3 Psoriasis guideline.

After 10 weeks of infliximab therapy (5 mg/kg of body weight at the usual intervals), 75 - 88 % of patients with moderate to severe psoriasis achieve PASI 75 (EL 1). Infliximab is one of the most effective treatments available for induction therapy in psoriasis vulgaris. Infliximab is also suitable for long-term therapy. Based on data from available studies, the efficacy of long-term therapy may diminish in some psoriasis patients after 24 weeks of treatment. The use of TNF-α antagonists can be especially useful in patients with psoriatic arthritis. There are also indications that infliximab may be suitable for the treatment of severe, rare forms of psoriasis.

Several safety aspects must be taken into consideration for the use of infliximab. The most important are infusion reactions and the risk of serious infection. This requires a careful assessment of the indications for its use, and thorough education and monitoring of the patient.

Given the vast number of patients who have been treated with infliximab (for other diseases as well), the risk of adverse effects is readily assessed.

The feasibility for the patient is good. For the doctor, the effort involved is increased by the need for infusion management.

Therapy should be given continuously every eight weeks in order to prevent more frequent infusion reactions as can occur with episodic administration.

Combination therapy with infliximab and MTX may help prevent the formation of antibodies.

Treatment recommendation

Infliximab is recommended for induction therapy in patients with moderate to severe psoriasis vulgaris, especially if other forms of therapy have failed to achieve sufficient treatment success or are contraindicated or not tolerated. ↑↑

Methotrexate

Table 19 Summary table

Methotrexate	
Approval in Germany	
Lantarel®	1991 (psoriasis vulgaris)
Metex® 7.5/10 mg	1992 (psoriasis vulgaris)
Metex® 2.5 mg	2004 (psoriasis vulgaris)
Recommended control parameters	Blood differential (Hb, Hct, blood differential, thrombocytes), kidney function (serum creatinine, urea, urine sediment), liver values (serum transaminase), amino-terminal propeptide of type III pro-collagen
Recommended initial dosage	7.5–15 mg/weekly
Recommended maintenance dosage	5–22.5 mg/weekly depending on effect
Onset of clinical effect	After 4–8 weeks
Response rate	PASI 75 in 25–50% of patients at the end of the induction phase of 16 weeks (EL 2)
Main contraindications	Liver dysfunction, pregnancy
Important UAEs (limited selection)	Liver fibrosis/cirrhosis, pneumonia/ alveolitis, bone marrow depression, renal damage, alopecia (reversible), nausea, weariness, vomiting, elevated transaminases, infection, gastrointestinal ulcerations, nephrotoxicity
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, sulfonylurea, tetracyclines, co-trimoxazol, chloramphenicol, dipyridamole, retinoids, ethanol, leflunomide
Misc.	Strict avoidance of alcohol, chest X-ray before treatment initiation

Instructions for application

Pre-treatment procedures

General measures

- Rule out acute infection
- If warranted based on patient history or clinical or laboratory signs, rule out HIV infection and viral hepatitis.

Specific measures

- Inform the patient on how to take the drug (only one day a week) and about early symptoms of potential adverse effects
- Physical examination, detection of skin changes typical of cirrhosis
- Liver ultrasound if needed, i.e., if there is a positive history or with detection of pathology during physical inspection
- Chest x-ray (for comparison later if any pulmonary changes occur during therapy)
- Measure serum levels of amino-terminal propeptide type III procollagen (PIIINP) before beginning treatment.

Measures during therapy

- Contraception (women as well as men undergoing treatment)
- Laboratory controls, see Table 20
- More frequent laboratory tests are needed when increasing dosage and in patients with an increased risk of elevated MTX levels (dehydration, diminished renal function, new drugs)
- Chest x-ray: with symptoms of acute fever, cough, dyspnea, and cyanosis; i m portant: MTX alveolitis
- MTX may be given with supplemental folates to reduce drug toxicity. A common treatment scheme is folate 5 mg the day after taking MTX.

Post-therapy measures

- Strict contraception for at least three months after therapy (men and women)

Table 20 Monitoring

Weeks → / Diagnosis ↓	Before treatment	1st month: 1 x/weekly	2nd - 3rd month: 1 x every 4 weeks	From 4th month onward: every 2 - 3 months
Blood differential[a]	X	X	X	X
Liver values[b]	X	X	X	X
Creatinine	X	X	X	X
Pregnancy test (urine)	X			
Liver ultrasound	X	[c]		
Chest x-ray	X			
Amino-terminal propeptide type III procollagen	X	[d]		

[a] Hb, Hct, erythrocytes, leukocytes, blood differential, thrombocytes
[b] ALAT, ASAT; AP , γGT, albumin, bilirubin, LDH
[c] Once yearly for dosages ≥15 mg/week
[d] Before treatment and every three months in 1st year, then 1x a year if available

Summary evaluation

In regard to the efficacy of methotrexate therapy in patients with psoriasis vulgaris 14 studies met the criteria for inclusion in the guidelines. [93,159,234,41,97,186,196,182,65,226,193,241,11,150,172] This includes six studies from the research for the European S3 psoriasis guideline. After 16 weeks of treatment with MTX 25 - 50 % of patients achieve PASI 75 (EL 2).
The maximum efficacy of MTX is not reached until after the induction phase, regardless of dosing scheme. MTX is suitable for long-term therapy.
The clinical experience with methotrexate is much greater than the documentation of its effectiveness and safety in clinical studies.
Clinical use of the drug is limited by severe adverse effects associated with its use as well as very rare, but serious idiosyncrasies.
Careful patient selection, thorough education of the patient, strict monitoring, use of the lowest possible effective dose (max. 22.5 mg/week), and additional use of folic acid or folinic acid allows for an acceptable safety profile for MTX.
Feasibility for the doctor and patient is limited by the need for careful monitoring of the patient during the induction phase.
Injection therapy is preferable due to individually variable bioavailability of orally administered MTX. MTX is suitable for use with TNF-α inhibitors. MTX may also be used in patients with concomitant psoriatic arthritis. Of all systemic agents, MTX has the lowest medication costs per day.

Treatment recommendation

MTX may be recommended for induction therapy in patients with moderate to severe psoriasis vulgaris. ↑

Retinoids

Table 21 Summary table

Acitretin	
Approval in Germany	1992 (Psoriasis vulgaris)
Recommended control parameters	Blood count, liver values, kidney values, blood lipids, glucose (initial), pregnancy test, X-ray controls of bone status in patients undergoing long-term therapy
Recommended initial dosage	0.3–0.5 mg/kg of body weight/daily for about 4 weeks, possibly followed by 0.5–0.8 mg/kg of body weight
Recommended maintenance dosage	Individual dosage depending on result and tolerability
Onset of clinical effect	After 4–8 weeks
Response rate	Highly variable and dose-dependent, partial remission (PASI 75) in 20–30% of patients (30–40 mg/daily) (EL 2)
Main contraindications	Kidney and liver damage, women of childbearing age who plan to have children, pregnancy, nursing
Important UAEs	Hypervitaminosis A, e.g., cheilitis, xerosis, nosebleed, alopecia, increased vulnerability of the skin
Important drug interactions	Phenytoin, tetracycline, methotrexate, alcohol, minipill
Misc.	Contraception up to 2 years after discontinuing the drug in women of childbearing age

Instructions for application

Pre-treatment procedures

- Rule out alcohol misuse
- Inform the patient that blood may not be donated during therapy and for up to one year afterward
- Ask about bone and joint pain
- Laboratory controls, see Table 22

Measures during therapy

- For long-term therapy (1-2 years): if symptoms warrant, exclude ossification by radiological examination of the spine and joints.
- For women of childbearing age: adequate contraception and avoidance of alcohol during treatment *
- Laboratory controls, see Table 22

Post-therapy measures

- Advise patients not to donate blood for up to one year after stopping therapy
- Women of childbearing age must ensure effective contraception * for up to two years after therapy
- Women of childbearing age should avoid alcohol consumption for up to two months after ending treatment

* The use of two contraceptive measures is advised: e.g., condom + pill; contraceptive coil/NuvaRing + pill. Important: avoid the use of low-dose progesterone preparations (minipill) during treatment and for 2 years after stopping treatment as their effectiveness is diminished by acitretin

Table 22 Monitoring

Weeks → Diagnosis ↓	Before treatment	1	2	4	8	12	16
Blood differential[a]	X				X		X
Liver enzymes[b]	X			X	X		X
Kidney values[c]	X						
Triglycerides, cholesterol, HDL[d]	X			X			X
Pregnancy test (urine) (monthly up to 2 years after therapy)	X			monthly			
Glucose (empty stomach)	X						

[a] Simple blood count (Hb, Hct, leukocytes, thrombocytes)
[b] ASAT, ALAT, AP, γGT
[c] Creatinine, urea
[d] Preferably measured twice on an empty stomach (2 weeks before and on the day of treatment initiation)

Summary evaluation

Out of 59 studies evaluated, eight meet the criteria for inclusion in the guidelines. [117,86,26,147,32,70,59,222] This includes studies on monotherapy and combination therapy (EL 2). Seven studies were included from the research for the European S3 Psoriasis Guidelines. The effectiveness of low-dose retinoids as monotherapy in moderate to severe psoriasis vulgaris is not satisfactory. After eight to 12 weeks, at a dosage of 0.4mg/kg of body weight to max. 40mg/daily, 23 - 30 % of patients achieve PASI 75 (EL 2). Although the drug is more effective at higher dosages, the related side effects are also often greater, with involvement of the skin and mucous membranes.
Use of the drug is limited in women of childbearing age due to the risk of birth defects, the need for monthly pregnancy tests, and having to ensure contraception for up to two years after stopping therapy.
One advantage of retinoids is their synergistic effects when used in combination with UV phototherapy. The data from the included studies are insufficient, however. The results of a paper by Gisondi et al. suggest potential synergistic effects in combination therapy with retinoids and TNF inhibitors, but larger studies are still needed.

Treatment recommendation

Due to its lacking efficacy, acitretin cannot be recommend as low-dose monotherapy.	↓
Acitretin cannot be recommended for women of childbearing age with plaque psoriasis.	↓

Ustekinumab

Table 23 Summary table

Ustekinumab	
Approval in Germany	January 2009 (psoriasis vulgaris)
Recommended control parameters	In week four, then every 8–12 weeks: blood count and differential, GOT, GPT, γGT
Recommended Initial dosage	45 mg (for >100 kg body weight: 90 mg) in weeks 0 and 4
Recommended maintenance dosage	45 mg (for >100 kg body weight: 90 mg) every 12 weeks
Onset of clinical effect	Six to 12 weeks; maximum efficacy after 24 weeks
Response rate	PASI 75 after 12 weeks 45 mg: 67% (EL 1) (PASI 75 after 12 weeks 45 mg in patients ≤100 kg body weight: 73–74%, PASI 75 after 12 weeks 90 mg in patients >100 kg body weight: 68–71%)
Main contraindications	Active tuberculosis or other serious infectious diseases
Important UAEs	Infections
Important drug interactions	No known interactions
Misc.	–

Instructions for application

Pre-treatment procedures
- Rule out acute infection
- Exclude tuberculosis based on current recommendations of the Paul Ehrlich Institute [51], see Appendix 1
- If warranted by patient history or clinical or laboratory signs, rule out HIV infection and viral hepatitis.
- Contraception must be ensured and pregnancy excluded in women of childbearing age
- Patients should be informed of the potential for serious and atypical infections and that they should seek prompt medical attention if symptoms occur.

Measures during therapy
- Monitoring for infection, if there is suspicion of infection, therapy should be discontinued, at least temporarily
- Interrupt therapy if pregnancy occurs
- Therapy must be administered by trained medical personnel

Post-therapy measures
- None

Table 24 Monitoring

Months → Diagnosis ↓	Before	1	2	3
Blood differential	X		Before each injection	
ASAT, ALAT, γGT	X		Before each injection	
Pregnancy test (urine)	X			
If infection is suspected, see pre-treatment procedures				

Summary evaluation
All three of the studies that were evaluated also met the criteria for inclusion in the guidelines. [127,167,77] All were grade A_2 studies, resulting in an evidence level of 1.
After being treated with ustekinumab 45 mg subcutaneously in weeks 0 and 4, 67 % of patients had at least a 75 % improvement in PASI score after 12 weeks (EL 1).
Ustekinumab is highly effective against psoriasis vulgaris during the induction phase. In some patients, the maximum effectiveness of the drug is not reached until after six months of treatment. Ustekinumab is suitable for long-term therapy.
At present, there are data from a few thousand patients. Based on these data, there is no indication of an increased risk of infection. For an assessment of long-term safety, larger patient samples are needed.
Therapy is feasible for the doctor and patient.

Treatment recommendation
Ustekinumab is recommended for induction therapy in adult patients with moderate to severe psoriasis vulgaris, especially if other therapies have been unsuccessful, are not tolerated, or are contraindicated. ⇑⇑

Other therapies

Climatotherapy

Table 25 Summary table

Climatotherapy	
Approval in Germany	More than 200 years of clinical experience with climate therapy
Recommended control parameters	Regular inspections of the skin
Recommended initial dosage	Therapy schemes vary by institution/treatment site
Recommended maintenance dosage	Therapy schemes vary by institution/treatment site
Onset of clinical action	Highly variable
Response rate	Highly variable (EL 3)
Main contraindications	Depend on chosen modality
Important UAEs	Depend on chosen modality
Important drug interactions	N/A
Misc.	–

Summary evaluation
Out of 39 evaluated studies, two met the criteria for inclusion in the guidelines (EG C). [43,90] The level of evidence is 3.
During a 1-4 week treatment regime at the Dead Sea, 55 % (two weeks) and 76 % (four weeks) of patients achieved PASI 75 (EL 3).
For combination therapy with natural phototherapy, the efficacy and safety of treatment are determined by the phototherapy component.
Climatotherapy is by definition performed in certain regions at specialized clinics.

Treatment recommendation
Climatotherapy, e.g., at the Dead Sea, may be recommended as part of integrated therapy in patients with a long history of psoriasis vulgaris. ⇑

Climatotherapy is not recommended for acute or short-term therapy. ⇓

Psychosocial therapy

Summary evaluation
Out of nine evaluated studies, three met the criteria for inclusion in the guidelines. [212,66,101] The resulting evidence level is 4.
The studies on the additive, psychosocial therapy of psoriasis patients were grade B and C studies; there was a significant selection bias and significant dropout rates. These factors make it impossible to draw any valid conclusions at this point on the efficacy of treatment.
One advantage of psychosocial therapy is the low number of adverse effects.
Psychosocial therapy in the form of psoriasis symptom management or patient education programs can have direct effects on skin symptoms, e.g., with improved stress management, as well as indirect effects on the development of psoriasis, e.g., with improved adherence / compliance.
Both of these treatment forms require further empirical study.

Treatment recommendation
The potential effects of disease on social, emotional, and psychological aspects of life should be considered in any patient with psoriasis. ⇑⇑

Patients should be informed of the availability of self-help groups. ⇑⇑

Patients should be informed about the possibility of participating in a structured education program according to the recommendations of the Working Group on Dermatological Prevention. ⇑⇑

Patients with a severely impaired quality of life, as well as repeated severe exacerbations of psoriasis vulgaris due to stress may be referred, if they wish, to a physician specialized in psychosomatic medicine and psychotherapy or specialized in psychiatry and psychotherapy, or to a psychotherapist or a physician who is also a qualified psychotherapist. ⇑⇑

Note on use of the guidelines

These guidelines are intended for use by dermatologists in private practice and by clinicians and other specialists involved in the treatment of patients with psoriasis vulgaris. An update of the patient version of the guidelines is currently underway. Finally, the guidelines also provide a guide for health insurers and policy-makers.

The description of selected therapies is intentionally restricted to the most relevant aspects in the opinion of the guidelines' expert committee. Those aspects that are not specific to a certain intervention, such as assessing drug intolerance or allergies, ruling out contraindications, etc. are not listed separately but are instead assumed to be a part of the physician's duty of care.

Physicians are advised to carefully read the package insert and manufacturer information and to determine whether dosage recommendations and other information contained in the guidelines, such as contraindications and drug interactions, is complete and current. Correct dosage and administration are solely the responsibility of the administering physician.

The authors and the publisher kindly ask readers to alert them to any apparent inaccuracies.

Like any science, the field of medicine is in constant flux. Our knowledge of present therapies as well as new treatment options is constantly growing. The utmost care was taken to ensure that the information contained in the guidelines was current at the time of their completion. The

reader is advised to keep abreast of current information after their publication.

Acknowledgments The update of the guidelines was generated upon request by the Deutsche Dermatologische Gesellschaft (DDG) and the Berufsverband Deutscher Dermatologen (BVDD). The project was supported by the 'Förderverein der Deutschen Dermatologischen Gesellschaft', the funding body of the DDG.

Conflict of interest The documentation and disclosure of potential conflicts of interest was based on the standardized form "Declaration of Conflicts of Interest" provided by the AWMF. The completed forms are available online at http://www.psoriasis-leitline.de. Given the diversity of the members of the guidelines group, it is assumed that any potential conflicts of interest balance each other out.

Appendix 1: Measures for excluding tuberculosis (scheme) modified after Diel et al. [51]

(1) Patient history	Immunosuppression
	Other risk factors for TB
	Prior LTBI/TB
	(Occupational) TB contact
	Origin
	BCG vaccine status
	TST/IGRA status
	Chest X-rays for comparison
(2) Clinical examination	
(3) Chest X-ray in two planes, CT of thorax if needed	If there are radiological signs of prior but inadequately or untreated TB without signs of activity, regardless of results of IGRA test:
	chemopreventive therapy with isoniazid (INH) for nine months
(4) IGRA test	IGRA negative:
	generally no chemoprevention
	IGRA positive:
	after ruling out the need for therapy: chemopreventive therapy with isoniazid (INH) for nine months
Complementary TST	If previous exposure to someone with infectious pulmonary TB is plausible despite negative IGRA tests and if BCG vaccine is unlikely given the patient's native country.
	Or for equivocal results on repeated IGRA test.
	Positive TST determines further procedures
Bacteriology if needed	

LTBI latent tuberculosis infection, *TB* tuberculosis, *TST* tuberculin skin test, *IGRA* Interferon-Gamma Release Assay

The Interferon-Gamma Release Assay (IGRA) is based on detection of INF-γ, which is secreted by T lymphocytes that are sensitized during a current or previous infection with mycobacterium tuberculosis (MTB).

The two commercially available IGRA tests that are sold in Germany use direct measurement of IFN-γ concentration in whole blood (QuantiFERON-TB® Gold In-Tube, Cellestis, Australia; QFT) or measurement of the number of IFN-γ secreting T lymphocytes from isolated peripheral mononucleated cells (PBMC; T-SPOT.TB®, Oxford Immunotec, Great Britain) [51].

Usually at least one of the tests is offered by routine diagnostic laboratories, or the samples are sent by the lab to one that does offer them. The QuantiFERON-TB® Gold In-Tube (QFT) test requires three special tubes coated with antigen which may be obtained from the respective laboratory.

For the T Spot.TB test, 8 ml of fresh, heparinized whole blood are needed from adult patient and at least 2–4 ml from children. Vacutainer Cell Preparation tubes or Standard Lithium Heparin tubes may be used. The sample must then be thoroughly shaken. For both tests, the samples may be transported at room temperature (QuantiFERON-TB® within 16 h/T Spot.TB test within 8 h).

For information on outpatient billing, see the resolution of the German Association of Physicians/Health Insurers (Arbeitsgemeinschaft Ärzte/Ersatzkassen), 255th session (written resolution) from 24 September 2010 on the addition of fee number 32670 in section 32.3.7 of chapter 32 of the German Physician Fee Schedule (E-GO) (Resolution No. 930) effective as of 1 January 2011, Dtsch Arztebl 2010; 107(42): A-2069/B-1801/C-1773. For inpatient billing, see OPS Code 1930.0.

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