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 noncompliance. 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].
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 phototherapies, and provide detailed descriptions of the administration and safety aspects.
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
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 ≥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 | 2002 (Atopic dermatitis, not approved for psoriasis vulgaris) |
| First approved in Germany | 2002 (Atopic dermatitis, not approved for psoriasis vulgaris) |
| Recommended initial dosage | Pimecrolimus: 1x to 2x daily |
| Recommended initial dosage | Tacrolimus: 1x to 2x 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 | Cave: Do not combine with phototherapy! Photoprotection! |

General assessment

Of the three studies with topical calcineurin inhibitors (pimecrolimus, tacrolimus) assessed, one study met the inclusion criteria of the Guidelines. 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.
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 | Recommended control parameters | Recommended initial dosage | Recommended maintenance dosage | Expected beginning of clinical effect | Response rate | Important contraindications | Important ADRs | Important drug interactions |
|-----------------|--------------------------|-------------------------------|---------------------------|-----------------------------|-------------------------------------|--------------|---------------------------|-----------------|---------------------------|
| Betamethasone dipropionate | 1956 (Psoriasis vulgaris) | None | One to two times daily | Gradual reduction following onset of effect | After 1–2 weeks | Betamethasone dipropionate, two times daily: marked improvement or clearance of the skin lesions in 46–56% patients after 4 weeks (LE 1) | Skin infections, rosacea, perioral dermatitis | Skin infections, perioral dermatitis, skin atrophy, hypertrichosis, striae | None |

**General assessment**

Of the 100 studies assessed for a monotherapy with corticosteroids, 20 fulfilled the Guidelines’ inclusion criteria.[17-36]

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 D₃ derivates.

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 telangiectases 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                  | 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 |
|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| First approved in Germany | After long-term application/application on large areas; if needed clinical controls for potential development of skin carcinoma                                                                                                                          |
| Recommended control parameters | 5–20% salve preparations or gels for local therapy, 1× daily                                                                                                                                                                 |
| Recommended initial 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. 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** |  |
| 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. 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 2x 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 |  |

**Vitamin D₃ and analogues**

**Table 6** Tabular summary

| Vitamin D₃ 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 D₃-analogues |

**General assessment**

Of the nine studies assessed, six fulfilled the Guidelines’ inclusion criteria. 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.
General assessment

Of the 39 studies considered, 11 fulfilled the Guidelines’ inclusion criteria. The majority of available data is on calcipotriol. After vitamin D₃-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 D₃-analogue is combined with topical corticosteroids during the initial therapy. In the treatment of severely affected patients, topical therapy with vitamin D₃-analogues demonstrated synergistic effects with a UV phototherapy and systemic cyclosporine therapy. The topical vitamin D₃-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 D₃-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 D₃-analogues with UV phototherapy or a systemic therapy can be recommended.

Phototherapy

Table 7 Tabular summary

| Phototherapy | Clinical experience, depending on the modality for >50 years |
|--------------|----------------------------------------------------------|
| First approved in Germany | Regular skin inspection (UV erythema) |
| Recommended control parameters | Individual dose depends on skin type; options: |
| Recommended initial dosage | • UVB: 70% of minimum erythema dose (MED) |
| | • Oral PUVA (photochemotherapy): 75% of the minimum phototoxic dose (MPD) |
| | • Bath/cream PUVA: 20–30% of MPD |
| 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/cm² or mJ/cm²). 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. 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 D₃-analogue 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 | Before 1 | 2 | 3 | 4 | 5 | 6 | 9 |
|------------------|----------|---|---|---|---|---|---|
| Complete blood count* | x | x | x | x | x | x | x |
| ALT, AST* | x | x |

* Hb (hemoglobin), HCT (hematocrit), erythrocytes, leukocytes, differential blood count, platelets
* 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. 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, urinanalysis |
| 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)
- 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, A ST        | x x x x x     |           |
| Pregnancy test (urine) | x |           |

**General assessment**

Of the four studies assessed, three fulfill the Guidelines’ inclusion criteria. 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)
- 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*                  | x      |   |   |   |
|                   | AST, ALT                               | x      |   |   |   |
|                   | Pregnancy test (urine)                 | x      |   |   |   |

*Hb, HCT, erythrocytes, leukocytes, differential blood count, platelets

General assessment

Of the seven studies evaluated, four fulfill the Guidelines’ inclusion criteria.1[10-11] 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:
- Status of skin and mucous membranes
- Signs of infection
- Neurological, gastrointestinal symptoms
- Blood pressure

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

Maximum total duration of therapy: 2 years

Expected beginning of clinical effect

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)

Absolute:

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)

Relative:

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/cm², concomitant application of other immunosuppressives, retinoids or long-term prior-therapy with methotrexate (MTX)
Table 14 continued

| 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) | Increase of the cyclosporine level (CYP3A inhibition) through: Allopurinol, calcium antagonists, amiodarone, antibiotics (macrolides, clarithromycin, josamycin, ponsinomycin, pristinamycin, doxycycline, gentamicin, tobramycin, tetracyclins, 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 anti-inflammatories |
| Specific interactions: Potassium-saving substances: increased risk of hyperpotassemia |
| Reduced clearance of: Digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (e.g. lovastatin), diclofenac |
| Increased risk of lympho-proliferative diseases in transplant patients. Increased risk of squamous cell carcinoma in psoriasis patients following excessive phototherapy. Only moderately effective in and not approved for psoriatic arthritis Also used successfully in the therapy of chronic-inflammatory diseases in children |

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 progestrone-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
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.

### 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 |
| Uric acid | x | x | x | x | x | x |
| Pregnancy test (urine) | x | | | | | |
| Cholesterol, triglyceride<sup>d</sup> | x | x | x | x |
| Magnesium<sup>e</sup> | x | x | x | x | x | x |

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

<sup>b</sup> ALT, AST, AP (alkaline phosphatase), γGT (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>[86, 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 D₃-analogaes or corticosteroids may allow a dose reduction of cyclosporine without a loss of efficacy.

### Table 16 Tabular summary

| Fumaric acid esters |
|---------------------|
| First approved in   | 1995 (Psoriasis vulgaris) |
| Germany             |                           |

| Recommended control parameters |
|--------------------------------|
| Serum creatinine, transaminases/γGT, complete blood count including differential blood count, urinanalysis |

| 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

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

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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

General assessment

Of 13 studies evaluated, nine fulfilled the Guidelines’ inclusion criteria. 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.

Table 18 Laboratory controls during treatment with fumaric acid esters

| Period in weeks | Pre-treatment | Month 1–6 | After month 6 |
|-----------------|---------------|-----------|--------------|
|                 |               | every 4 weeks | every 8 weeks |
| Complete blood count | x | x | x |
| ALT, AST, γGT | x | x | x |
| Serum creatinine | x | x | x |
| Urinalysis | x | x | x |

* Leukocytes, platelets, erythrocytes, differential blood count
### Methotrexate

#### Table 19 Tabular summary

| Methotrexate                                      |  
|--------------------------------------------------|
| First approved in Germany                        |  
| Lantarel® 1991 (Psoriasis vulgaris)              |  
| Metex® 7.5/10 mg 1992 (Psoriasis vulgaris)       |  
| Metex® 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)  |  
| Absolute contraindications:                      |  
| 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 |  
| Relative contraindications:                      |  
| 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 |  
| 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, phenyoitoin, retinoids, sulfonamides, sulfonlyurea, tetracyclines, co-trimoxazol, chloramphenicol, dipyrudamo, retinoids, ethanol, leflunomide |  
| Other                                            |  
| Consistent avoidance of alcohol. X-ray of the lungs prior to beginning therapy |  

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
- **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
- 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 | 1st month | 2nd – 3rd month | After 4th month |
|-----------------|-------------|-----------------|-----------|----------------|----------------|
|                 |             |                 | 1×/week   | 1×/2 weeks     | every 2–3 months |
| Complete blood count | x           |                 | x         | x              | x              |
| Liver values | x           |                 | x         | x              | x              |
| Creatinine/urine | x           |                 | x         | x              | x              |
| Urine sediment | x           |                 | x         | x              | x              |
| Pregnancy test (urine) | x           |                 |           |                |                |
| Liver sonography | x           |                 |           |                |                |
| Chest X-ray | x           |                 |           |                |                |
| Hepatitis B, C serology | x           |                 |           |                |                |
| Type III procollagen amino terminal propeptide (PIIINP) | x           |                 |           |                |                |

---

**General assessment**

Of 11 MTX monotherapy studies assessed for efficacy in psoriasis vulgaris, three studies fulfilled the Guidelines’ inclusion criteria.\[123, 128, 139\]

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\(^a\) (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\(^a\) 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\(^a\) 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

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

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 teratogenity, 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. 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. 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.

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**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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**Conflicts of interests**

All authors have filled in specific forms to declare their conflicts of interests. These forms are available online under www.psoriasis-leitlinie.de. The experts involved in drawing up these guidelines received no payments for their work other than travel expenses.

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