European Dermatology Forum

Systemic Treatment of Psoriasis vulgaris.

Developed by the Guideline Subcommittee of the
European Dermatology Forum

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European S3-Guidelines on the systemic treatment of psoriasis vulgaris

Supported by the EDF/EADV/IPC

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Table of contents

List of abbreviations

AGREE	**Appraisal of Guidelines Research & Evaluation**
ADR	**Adverse drug reaction**
BBUVB	**Broadband UVB**
BIW	**Biweekly**
BSA	**Body Surface Area**
BW	**Body weight**
CSA	**Ciclosporin**
dEBM	**Division of Evidence Based Medicine**
DLQI	**Dermatology Life Quality Index**
EADV	**European Academy of Dermatology and Venereology**
EDF	**European Dermatology Forum**
EOW	**Every other week**
GE	**Grade of evidence**
IM	**Intramuscular**
IPC	**International Psoriasis Council**
ITT	**Intention-to-treat**
IV	**Intravenous**
MED	**Minimal erythema dose**
MOP	**Methoxypsoralen**
MPD	**Minimal phototoxic dose**
MTX	**Methotrexate**
NBUVB	**Narrowband UVB**
NYHA	**New York Heart Association**
PASI	**Psoriasis Area and Severity Index**
PASI 50/75/100	**50/75/100 per cent improvement from baseline PASI**
PDI	**Psoriasis Disability Index**
PGA	**Physician´s Global Assessment**
sPGA	**Static Physician´s Global Assessment**
SC	**Subcutaneous**
TL01	**UVB 311 nm**

1 Introduction to the guidelines

1.1 Needs analysis/problems in patient care

Pathirana/Nast/Rzany

Psoriasis vulgaris is a common dermatologic disease, with an incidence in Western industrialized countries of 1.5% to 2%[1]. In more than 90% of cases the disease is chronic [1].

Patients with psoriasis vulgaris have significantly impaired quality of life. Depending on its severity, the disease can lead to a substantial burden in terms of disability or psychosocial stigmatization [2]. Indeed, patient surveys have shown that the impairment in quality of life experienced by patients with psoriasis vulgaris is comparable to that seen in patients with type 2 diabetes or chronic respiratory disease [3].

Patients are often dissatisfied with current therapeutic approaches, and their compliance is poor. Patient surveys have shown that only about 25% of psoriasis patients are completely satisfied with the success of their treatment, while over 50% indicate moderate satisfaction and 20% slight satisfaction [4]. The rate of non-compliance with systemic therapy is particularly high, ranging up to 40% [5]. In addition to limited efficacy and poor tolerance, explanations for these figures include fear and a lack of information among patients regarding adverse events (e.g. due to perceived poor communication between patients and physicians).

Frequently, in settings where high-level (i.e. evidence-based) guidelines are lacking, therapeutic strategies are not based on evidence. Moreover, there are major regional differences in the use of the various therapeutic approaches. Experience has shown that the choice of treatment for patients with psoriasis vulgaris is often made according to traditional concepts, without taking into consideration the detailed, evidence-based knowledge currently available regarding the efficacy of individual treatment options. In addition, physicians are frequently hesitant to administer systemic therapies, both because of the added effort involved in monitoring patients for adverse events and, in some cases, due to the risks of multiple interactions with other drugs [6].

1.2 Goals of the guidelines/goals of treatment

Mrowietz/Reich

Treatment goals in psoriasis

Guidelines for the treatment of psoriasis provide an overview of a variety of practical aspects relevant to selecting drugs and monitoring patients on therapy [7-11]. Based on the evaluation of efficacy and safety data, as well as on the practical experience obtained with different treatment modalities, they contain a range of recommendations reached in a structured consensus process.

Epidemiological studies conducted in Germany and other countries, as well as the results of patient surveys in Europe and the United States, have indicated that mean disease activity in patients with psoriasis is high and quality of life is poor, even among patients who are seen regularly by dermatologists; moreover, these findings are accompanied by data showing low treatment satisfaction and a demand for more efficacious, safe, and practical therapies [12-15].

Although there are no generally accepted treatment goals in psoriasis patients at present, a number of concepts have emerged from the ongoing discussion. These, together with the present guidelines, may help dermatologists decide when and how to progress along existing treatment algorithms, ultimately improving patient care. These concepts are based on a selected list of outcome measures that take into account not only the severity of skin symptoms but also the impact of disease on health-related quality of life (HRQoL).

Although it has its drawbacks, the most established parameter to measure the severity of skin symptoms in psoriasis is the Psoriasis Area and Severity Index (PASI), which was first introduced in 1978 as an outcome measure in a retinoid trial [16]. The PASI is also part of most currently used classifications of disease severity in psoriasis [17] and represents a necessary first step in selecting a treatment strategy. In recent clinical trials, especially those investigating biological therapies, the most commonly used primary efficacy measure has been the PASI 75 response, i.e. the percentage of patients who at a given point in time achieve a reduction of at least 75% in their baseline PASI. Because this parameter (or an equivalent response criterion) is reported in many trials on systemic therapies for psoriasis, and because a PASI 75 response is now widely accepted as a clinically meaningful improvement, it also serves as the central evidence-based efficacy parameter in these and other psoriasis treatment guidelines. It should also be noted that a PASI 75 response, as is documented in these guidelines, can be achieved in the majority of patients with the therapeutic armamentarium presently available for the

treatment of moderate to severe disease. Therefore, although the complete clearance of skin lesions may be regarded as the ultimate treatment goal for psoriasis, a PASI 75 response has been proposed as a treatment goal that is both practical and realistic [18]. Based on the data available from clinical trials, this goal should be assessed between 10 and 16 weeks after the initiation of treatment, i.e. the time during which PASI responses were typically evaluated as the primary outcome measure (Table 1). There is evidence that some patients may reach a PASI 75 response at a later time (i.e. between 16 and 24 weeks of therapy), especially when treated with drugs such as methotrexate, the fumaric acid esters, etanercept, or efalizumab.

HRQoL is an important aspect of psoriasis, not only in defining disease severity but also as an outcome measure in clinical trials. The Dermatology Life Quality Index (DLQI) is the most commonly used score for assessing the impact of psoriasis on HRQoL. It consists of a questionnaire with 10 questions related to symptoms and feelings, daily activities, leisure, work and school, personal relationships, and bother with psoriasis treatment [19]. The DLQI is assessed as a score ranging from 0 to 30, and the meaning of the absolute DLQI has been categorized and validated into bands [20]. These bands describe the overall impact of skin disease on a person's HRQoL as follows: 0-1 = "no effect"; 2-5 = "small effect"; 6-10 = "moderate effect"; 11-20 = "very large effect"; 21-30 = "extremely large effect." Another study demonstrated that a change of five points in the DLQI correlates with the minimum clinically meaningful change in a person's HRQoL [21]. Although there is no correlation between absolute PASI and absolute DLQI scores [12], there seems to be a correlation between an improvement in PASI and an improvement in the DLQI. The drugs that produce the highest PASI reduction by the end of induction therapy are also associated with the greatest reduction in DLQI [22]. A DLQI of 0 or 1 has been proposed as a treatment goal [18] and indicates that the HRQoL of the patient is no longer affected by psoriasis (Table 1).

In daily practice, it may be useful to define a second set of treatment goals that serve as "lowest hurdles" (i.e. a minimum of efficacy that should be achieved). If these goals are not met, a treatment should be regarded as inefficient and must consequently be stopped and replaced by another treatment option. A PASI 50 response and DLQI <5 have been proposed as a potentially useful minimum efficacy goal. [18]. Treatment goals should be monitored at appropriate intervals during long-term maintenance therapy (e.g. at 8-week intervals).

Additional treatment goals may be required in individual patients, such as those with joint or nail involvement or with other psoriasis-related co-morbidities.

Table 1: Proposal for treatment goals in psoriasis [adapted from [18]].

	Skin symptoms	HRQoL
Treatment goals (assessment after 10 to 16 weeks, and every 8 weeks thereafter)	PASI 75 or, alternatively, PGA of "clear" or "almost clear"	DLQI of 0 or 1
Minimum efficiency; "lowest hurdle"	PASI 50	DLQI <5 or, alternatively, DLQI improvement of at least 5 points

1.3 Notes on the use of these guidelines

Pathirana/Nast/Rzany

These guidelines are intended for dermatologists in the clinic and in private practice, as well as for other medical specialists involved in the treatment of psoriasis vulgaris. Furthermore, they are meant to serve as an aid for health insurance organizations and political decision-makers.

Discussions of the different therapeutic approaches have been deliberately restricted to aspects that the experts felt were especially relevant. Steps that can be considered part of every physician's general obligations when prescribing drugs (e.g. inquiring about allergies and intolerance reactions, as well as identifying potential contraindications) are not listed individually. Furthermore, all patients should be informed about the specific risks associated with any given systemic therapy.

Readers must carefully check the information in these guidelines and determine whether the recommendations contained therein (e.g. regarding dose, dosing regimens, contraindications, or drug interactions) are complete, correct, and up to date. The authors and publishers can take no responsibility for dosage or treatment decisions taken in this rapidly changing field. All physicians following the recommendations contained in these guidelines do so at their own risk. The authors and the publishers kindly request that readers inform them of any inaccuracies they may find.

As with all fields of scientific inquiry, medicine is subject to continual development, and existing treatments are always changing. Great care was taken while developing these

guidelines to ensure that they would reflect the most current scientific knowledge at the time of their completion. Readers are nevertheless advised to keep themselves abreast of new data and developments subsequent to the publication of the guidelines.

1.4 Methodology

Spuls/Ormerod/Smith/Saiag/Pathirana/Nast/Rzany

A detailed description of the methodology employed in developing the guidelines can be found in the methods report.

Base of the guidelines

The three existing evidence-based national guidelines (GB, NL, DE) for the treatment of psoriasis vulgaris were compared and evaluated by a group of methodologists using the standard international Appraisal of Guidelines Research and Evaluation (AGREE) instrument. The group decided that all three guidelines fulfilled enough criteria to be used as the base for the new evidence-based European guidelines on psoriasis [23].

Database and literature search

The literature evaluated in the existing national guidelines serves as the basis for the present set of European guidelines. In cases where the national guidelines differed in terms of the grade of evidence they assigned to a particular study, this study was re-evaluated by the abovementioned group of methodologists. For the systemic interventions covered by the national guidelines, and for novel systemic interventions, a new literature search, encompassing studies published between May 2005 and August 2006, was conducted using MEDLINE, EMBASE, and the Cochrane Library. To ensure a realistic evaluation of the biologics covered in these guidelines, an additional search was performed for these interventions, with an end date of 16 October 2007. Altogether, searches were performed for the following systemic interventions: methotrexate, ciclosporin, retinoids, fumaric acid esters, adalimumab, infliximab, etanercept, alefacept, and efalizumab. Ustekinumab was not part of these guidelines due to the end date of the literature search. This drug will be included in the update of the guidelines. Combination therapy was not included in the search.

Evaluation of the literature

The evaluation of the literature focused on the efficacy of the different interventions in the treatment of plaque psoriasis. After a preliminary review of the literature, each study identified as potentially relevant was appraised by one methodologist using a standardized

literature evaluation form (LEF). A second appraisal was conducted by a member of the dEBM. If the two appraisals differed, the study was reassessed. A total of 678 studies were evaluated, 114 of which fulfilled the criteria for inclusion in the guidelines. Studies were included if they fulfilled the methodological quality criteria specified on the literature hevaluation form (for details see appendix I, LEF and the Guidelines Methodology Report). Studies that did not meet these criteria were excluded.

Other aspects of the interventions (e.g. safety and combination therapy) were evaluated by the participating experts based on their many years of clinical experience and in accordance with the publications available, but without conducting a complete, systematic review of the literature.

Evidence assessment

To asses the methodological quality of each study included for efficacy analysis, a grade of evidence was assigned using the following criteria:

Grades of evidence

A1 Meta-analysis that includes at least one randomized clinical trial with a grade of evidence of A2; the results of the different studies included in the meta-analysis must be consistent.

A2 Randomized, double-blind clinical study of high quality (e.g. sample-size calculation, flow chart of patient inclusion, ITT analysis, sufficient size)

B Randomized clinical study of lesser quality, or other comparative study (e.g. non-randomized cohort or case-control study).

C Non-comparative study

D Expert opinion

In addition, the following levels of evidence were used to provide an overall rating of the available efficacy data for the different treatment options:

Levels of evidence

1 Studies assigned a grade of evidence of A1, or studies that have predominantly consistent results and were assigned a grade of evidence of A2.

2 Studies assigned a grade of evidence of A2, or studies that have predominantly consistent results and were assigned a grade of evidence of B.

3 Studies assigned a grade of evidence of B, or studies that have predominantly consistent results and were assigned a grade of evidence of C.

4 Little or no systematic empirical evidence; extracts and information from the consensus conference or from other published guidelines.

Therapeutic recommendations

For each intervention, a therapeutic recommendation was made based on the available evidence and other relevant factors. The recommendations are presented in text form, rather than using scores or symbols (e.g. arrows) to highlight the strength of the recommendation. For the statements on efficacy, the following scale was agreed upon, based on the PASI results of the included studies for each intervention:

PASI 75 >60%: intervention recommended

PASI 75 30-60%: intervention suggested

PASI 75 <30%: intervention not suggested

Please note that these guidelines focus on induction therapy. Therefore the relevant PASI improvements are based on the results observed after a period of 12 to 16 weeks. Maintenance therapy was not the focus of these guidelines.

Key questions

A list of key questions concerning the different systemic therapies was compiled by the guidelines group. After the group graded the importance of each question using a separate Delphi procedure, a revised list of questions was distributed to the authors of the individual chapters. The authors subsequently answered the questions relevant to their chapter in the various subchapters of their sections. Some of the relevant questions were also subject to consensus (see below).

Choice of sections requiring consensus

The guidelines group designated particularly important sections as those requiring consensus (e.g. the Therapeutic Recommendations and Instructions for Use sections).

Consensus process

The consensus process consisted of a nominal group process and a DELPHI procedure.

Nominal group process

The sections requiring consensus were discussed by the entire guidelines group following a formal consensus process (i.e. nominal group technique). The discussion took place during a consensus conference that was moderated by a facilitator.

DELPHI Procedure

The DELPHI procedure was carried out on the consensus sections of chapters that could not be discussed at the consensus conference due to time constraints. The primary suggestions to be voted on were made by the authors of the corresponding chapters. The members of the consensus group received the texts by e-mail. Voting was done by marking the preferred statement or statements with an X. If suggestions were found to be incomplete, new suggestions could be added by any member of the group. The new suggestions were put to vote during the next round. Altogether, three voting rounds were conducted. A passage was regarded as consented when at least a simple consensus (i.e. agreement by ≥75% of the voting experts) was reached. Passages for which no consensus could be reached are clearly marked with an asterisk and a corresponding explanation.

Harmonization of the chapters on biologicals

To decrease discrepancies in the biological chapters regarding clinically important topics, such as TBC testing, vaccination, and malignancy risk, these subchapters were harmonized. The statements in each biologics chapter referring to these topics were summarized and forwarded to the authors of these chapters. In close cooperation with the authors, harmonised statements for the abovementioned topics were developed and added to the respective subchapters.

External review

By experts

According to the AGREE recommendations on the quality assessment of guidelines, an external review of the guidelines was conducted. The experts for this review were suggested by the guidelines group and were as follows:

- Michael Bigby (USA)
- Robert Stern (USA)
- Paul Peter Tak (Netherlands)

By the national dermatological societies

Furthermore, according to the EDF Standard Operation Procedure, all European dermatological societies were invited to review the guidelines text prior to the last internal review. The comments from the participating societies were forwarded to the chapter authors and considered during the last internal review.

Update of the guidelines

These guidelines will require updating approximately every five years. Because new interventions, especially in the field of biologics, may be licensed before this five-year interval has expired, the EDF's subcommittee on psoriasis will assess the need for an earlier update for specific (or all) interventions.

2 Introduction to psoriasis vulgaris

Mrowietz/Reich

Psoriasis is one of the most common inflammatory skin diseases among Caucasians worldwide. With its early onset – usually between the ages of 20 and 30 – as well as its chronic relapsing nature, psoriasis is a lifelong disease that has a major impact on affected patients and society. Patients with psoriasis face substantial personal expense, strong stigmatization, and social exclusion. Management of psoriasis includes treatment, patient counselling, and psychosocial support.

Epidemiology

Plaque-type psoriasis is the most common form of the disease, with a prevalence of approximately 2% in Western industrialized nations. Non-pustular psoriasis has been classified into two types: type 1 psoriasis, which is characterized by early disease onset (i.e. usually before the age of 40), a positive family history, and an association with HLA-Cw6 and HLA-DR7; and type 2 psoriasis, which is characterized by a later disease onset (i.e. usually after the age of 40), a negative family history, and a lack of any prominent HLA association.

Several other chronic inflammatory conditions, including Crohn's disease, are more frequent in patients with psoriasis, which supports the notion of common disease pathways. In addition, psoriasis – like other chronic inflammatory conditions – is associated with a specific pattern of comorbidities that are believed to be at least partially related to the systemic inflammatory nature of these diseases. For example, metabolic syndrome (i.e. low HDL cholesterol, elevated triglycerides, elevated serum glucose, and hypertension in patients with obesity) is frequently observed in patients with psoriasis. These comorbidities potentially increase cardiovascular risk in patients with psoriasis and contradict the previously held belief that patients do not die from this disease. Epidemiological studies have shown, for example, that a 30-year-old patient with severe psoriasis has a threefold increased risk of myocardial infarction [24]. Mortality due to myocardial infarction or stroke is approximately 2.6 times higher in patients with early or frequent hospitalization for psoriasis [25], and the life expectancy of patients with severe psoriasis, after adjusting for relevant confounding factors, is approximately three to four years less than that in individuals without psoriasis [26].

About 20% of patients with psoriasis develop a characteristic type of inflammatory arthritis called psoriatic arthritis.

Genetics

Plaque-type psoriasis shows a multi-factorial, polygenetic pattern of inheritance. A number of susceptibility genes (*PSORS 1-9*) have been identified as contributing to disease predisposition, the most prominent of which is a locus on chromosome 6p21 (*PSORS 1*). Several genetic variations associated with psoriasis have also been identified, including polymorphisms of the genes encoding for tumour necrosis factor α (TNF-α), interleukin (IL)-12/23 p40, and the IL-23 receptor [27, 28].

Trigger factors may be involved in the first manifestation of psoriasis, or contribute to disease exacerbation; these include streptococcal infections, stress, smoking, and certain drugs, such as lithium and beta-blockers [29-31].

Pathogenesis

Psoriasis is the result of a complex cutaneous immune reaction with a major inflammatory component involving elements of the innate and adaptive immune systems and abnormal keratinocyte proliferation and differentiation. Activation of antigen-presenting cells leads to the preferential development of Th1- and Th17-type T cells that migrate into and proliferate within the skin. Homing mechanisms involve a variety of surface receptors and chemotactic factors, such as IL-8 and the cutaneous T-cell-attracting cytokine (CCL27). Several mediators have been identified that orchestrate many of the changes typical of psoriasis, including IL-12 and IL-23, TNF-α, and interferon γ (IFN-γ). In addition to epidermal hyperparakeratosis; angiogenesis leading to capillary abnormalities in the upper dermis; and a lymphocytic infiltrate, the histopathological changes seen in psoriasis include a marked influx of neutrophils, which may form sterile abscesses in the epidermis (i.e. so-called Munro's microabscesses).

Clinical features

Plaque-type psoriasis

Plaque-type psoriasis, which is the focus of these guidelines, is the most common clinical form of the disease, accounting for more than 80% of all clinical cases. This variant is characterized by sharply demarcated erythematous and scaly plaques, typically at the extensor surfaces of the extremities. Lesions may be stable for a long time, or progress to involve larger areas of the body.

Guttate psoriasis

Guttate psoriasis presents with small, widely distributed erythematous papules with mild scales. It is often the first clinical manifestation of psoriasis, especially when the onset is triggered by a streptococcal infection. A later transition to plaque psoriasis is possible.

Intertriginous psoriasis

Plaques located exclusively or almost exclusively in the larger skin folds of the body (axilla, abdominal folds, submammary area, and inguinal/gluteal clefts) define the clinical picture of intertriginous psoriasis.

Inverse psoriasis

Patients affected by the rare inverse type of psoriasis have plaques primarily in the flexural areas without concomitant involvement of the typical predilection sites (i.e. the extensor surfaces).

Pustular psoriasis

Pustular psoriasis presents as different clinical subtypes. The generalized occurrence of initially scattered, subsequently confluent pustules together with fever and generalized lymphadenopathy is known as generalized pustular psoriasis (also know as von Zumbusch psoriasis).

Palmoplantar pustulosis

Palmoplantar pustulosis is a genetically distinct disease that may represent an independent disease entity. It is characterized by fresh yellow and older brownish pustules that appear exclusively on the palms and/or soles.

Acrodermatitis continua suppurativa (Hallopeau)

Pustules with severe inflammation on the tips of the fingers and/or toes, often rapidly leading to damage to the nail matrix and nail loss, are the clinical characteristics of this rare variant of pustular psoriasis. The distal phalanges may be destroyed during the course of the disease.

Diagnostic approach

The diagnosis of psoriasis vulgaris is based almost exclusively on the clinical appearance of the lesions. Auspitz's sign (i.e. multiple fine bleeding points when psoriatic scale is removed) may be elicited in scaly plaques. Involvement of predilection sites and the presence of nail psoriasis contribute to the diagnosis. Occasionally, psoriasis is difficult to distinguish from nummular eczema, tinea, or cutaneous lupus. Guttate psoriasis may resemble pityriasis rosea. In rare cases, mycosis fungoides must be excluded. If the skin changes are located in the intertriginous areas, intertrigo and candidiasis must be considered. In some cases, histological examination of biopsies taken from the border of representative lesions is needed to confirm the clinical diagnosis.

Severity assessment

Tools for assessing the severity of symptoms are available for plaque psoriasis. The most widely used measure is the Psoriasis Area and Severity Index (PASI). According to recent guidelines, moderate to severe disease is defined as a PASI score >10 [32]. PASI 75 and PASI

90 responses are dynamic parameters that indicate the percentage of patients who have achieved an at least 75% or 90% improvement in their baseline PASI score during treatment. Other measures frequently used to quantify disease severity in psoriasis are the Physician´s Global Assessment of disease severity (PGA), which is based on the measures also encompassed in the PASI; and body surface area (BSA), which represents the percentage of the body surface affected by psoriasis.

Quality of life

Different questionnaires have been developed to measure the impact of psoriasis on health-related quality of life (HRQoL); these differ from one another based on their generic (SF-36), disease-specific (DLQI, Skindex), or psoriasis-related (PsoQol, PDI) approach.

Biopsychosocial aspects of psoriasis

Maccarone/Richards

The recognition of psychological needs in patients with psoriasis is critical for managing the condition. The biopsychosocial model emphasizes the need for physicians to focus not only on the physical but also on the psychological and social components of the disease. Increasing evidence suggests that both clinical and psychological outcomes are optimized when patients' emotional concerns are addressed.

The psychological impact of psoriasis has been subject to a recent major review highlighting the potential for significant psychological and social morbidity in affected patients [33]. There is significant empirical evidence to support patients' accounts of the wide-ranging effects of psoriasis on their social and interpersonal relationships [14], everyday activities [13], and their own family and mental health [34, 35]. Although estimates regarding the levels of clinically relevant distress vary, generally about 20% to 25% of patients with psoriasis attending outpatient clinics will experience clinically significant psychological distress [33, 34], including depression [36-38] and anxiety [38]. The extent of this distress can be seen clearly from research that has identified active suicidal ideation in 5.5% and wishes to be dead in approximately 10% of patients with psoriasis [39].

The consequences of psoriasis on patients' quality of life are well established. Studies have demonstrated that patients with psoriasis experience impairments in quality of life or health status comparable to those seen in other major conditions, such as cancer and heart disease [3]; achieve lower scores on quality-of-life and disability assessments than healthy controls [40]; and

are prepared to incur considerable costs for a cure [41]. Moreover, the physical and emotional effects of psoriasis have been shown to have a significantly negative impact on patients' occupational function, with one study reporting that approximately 25% of patients with psoriasis have missed work or school due to their condition [13].

Individuals with psoriasis often report interpersonal concerns related to their condition, such as embarrassment if psoriasis is visible [14] and, in 27% to 40% of patients, difficulties with sexual activities [13, 14, 42]. Perceived stigmatization is also widely documented in patients with psoriasis and has been shown to be significantly related to psychological distress [43], disability [38], and quality of life [44]. Moreover, stigmatized individuals have been shown to be more distressed about symptoms and to report a greater interpersonal impact and a lower quality of life than their non-stigmatized counterparts [45].

Interestingly, the clinical severity of psoriasis is not a reliable predictor of the severity of psychological distress, disability, or impairment in quality of life [13, 33, 38]. Moreover, studies employing robust psychometric assessments have demonstrated that physician-rated improvements in clinical severity (e.g. PASI) do not necessarily lead to a reduction in the psychological distress experienced by patients [46]. The relationship between disease severity and psychological outcome appears to be mediated by factors such as the beliefs patients hold about their condition in relation to its consequences; perceived control; the demands of the condition; and the perceived helpfulness of social support [47]. Such studies highlight the importance of routine inquiry into the psychosocial impact of psoriasis for patients, rather than relying on indicators of clinical severity as a reflection of potential psychological distress.

Empirical evidence suggests that the effectiveness of conventional treatments can be affected by psychological distress [48]. As a result, it is unlikely that simply treating the signs and symptoms of psoriasis will be the most effective treatment approach. Research has shown that adjunctive psychological interventions enhance the effectiveness of standard treatments [49-51]. For example, patients who opted for a psoriasis-specific cognitive-behavioural intervention in addition to standard treatment showed significantly greater reductions in unhelpful beliefs about the condition, as well as in anxiety, depression, disability, stress, and physician-rated clinical severity of disease, compared with patients who received standard care [49, 50].

Regardless of the positive benefits of psychological interventions [49-51], it is important to note that not all patients are willing to participate in them. Factors such as increased worry,

anxiety, and feelings of stigmatization can all impede attendance [52]. Both patients and physicians need to be informed about the potential benefits of such approaches to clinical management so as to optimize patient care. Moreover, research has shown that the ability of dermatologists to identify distress in patients is unsatisfactory, and that in cases where physicians did identify patients as distressed, referral to appropriate services was made in only one third of cases [53].

Not all primary or secondary care centres have access to psychological services. However, patients can be offered a stepped-care approach that draws support from medical and nursing staff. Dermatologists can inform patients and encourage them to seek support from local psoriasis patient associations [13], which can provide information on many aspects of living with psoriasis that patients can subsequently share with key individuals around them, including colleagues and family members. This, in turn, may help promote increased awareness and understanding of the condition, thus facilitating more helpful approaches to patients by others. At the simplest level, the dermatologist can employ an empathic approach that takes proper account of both the physical aspects of the disease and the psychosocial issues affecting the patient. In doing so, a more collaborative approach will be fostered in the management of the condition.

3 Systemic therapy

3.1 Methotrexate

Karvonen/Barker/Rantanen

Introduction/general information

Methotrexate has been used in the treatment of psoriasis since 1958 [54], and is widely employed in Europe. In dermatology, methotrexate is used most frequently for the treatment of moderate to severe plaque-type psoriasis, especially in cases with joint involvement or in pustular or erythrodermic forms [55]. The drug is also commonly used in the management of other chronic inflammatory diseases, such as rheumatoid arthritis. It is available in all European countries. The other main indication is antineoplastic chemotherapy, albeit with different dosing regimens. To minimize the incidence of potential side effects and to maintain optimal therapeutic efficacy when initiating and subsequently monitoring therapy, a detailed history, examination, and various laboratory investigations are indicated.

Table 2: Tabular summary

Methotrexate	
Approval for psoriasis	1958
Recommended controls	Blood count, liver enzymes, creatinine, urine sediment, pregnancy test (urine), HBV/HCV, serum albumin, PIIINP, chest X-ray (at the beginning of therapy)
Recommended initial dose	5-10 mg weekly
Recommended maintenance dose	5-30 mg weekly (can be dosed orally, subcutaneously, or intramuscularly)
Clinically significant response expected after	4-12 weeks
Response rate	PASI 75 in 60% of patients after 16 weeks
Absolute contraindications	Severe infections, severe liver or kidney disorders, bone marrow dysfunction, pregnancy or breastfeeding, impaired lung function or pulmonary fibrosis, alcohol abuse, immunodeficiency, acute peptic ulcer
Important side effects	Bone marrow depression, liver toxicity, pneumonia, and alveolitis
Important drug interactions	Trimethoprime, probenecid, retinoids, NSAIDs
Special considerations	Dosage only once weekly; overdose may lead to leucopenia/pancytopenia and thus be life threatening

Mechanism of action

Methotrexate (4-amino-10-methylfolic acid, MTX), an analogue of folic acid, competitively inhibits the enzyme dihydrofolate reductase and several other folate-dependent enzymes. The main effect of methotrexate is the inhibition of thymidylate and purine synthesis, resulting in decreased synthesis of DNA and RNA. Inhibition of nucleic acid synthesis in activated T cells and in keratinocytes is believed to account for the antiproliferative and immunomodulatory effects of methotrexate, which are considered the main mechanisms of the therapeutic effect of methotrexate in psoriasis vulgaris. Methotrexate enters the cell through the reduced folate carrier and is rapidly modified by the addition of up to six glutamates, forming pharmacologically active MTX-Glu_n.

After oral dosing, the maximum serum concentration is reached within 1 to 2 hours. Mean oral bioavailability is 70%, but may range from 25% to 70%. After intramuscular

administration, maximum serum concentration is reached within 30 to 60 minutes. Only a small fraction of methotrexate is metabolized, and the main route of elimination is through the kidney.

Dosing regimen

Methotrexate is administered once weekly, orally or parenterally (intramuscular or subcutaneous), for the treatment of psoriasis vulgaris. For oral administration, it is possible to take the weekly dose on one occasion (up to 30 mg) or to divide this dose into three individual doses, which are taken at 12-hour intervals over a 24-hour period. The latter approach is designed to reduce toxicity and side effects [56]; however, there is no clear evidence that this regimen is better tolerated. The initial dose should be 5 to 10 mg; subsequently, the dose should be increased depending on the response. Recommendations are that the maximum dose for the treatment of psoriasis vulgaris should not exceed 30 mg per week. All decimal points of prescribed doses should be written very clearly, because overdose may happen easily if, for example, daily dosage is used. In the elderly, the test dose should be reduced to 2.5 mg; the elderly and individuals with renal impairment are more likely to accumulate methotrexate. Methotrexate is a slow-acting drug, and it may take several weeks to achieve the complete clinical response for any given dose. There is some evidence that the combination of methotrexate with folic acid may reduce adverse reactions without affecting efficacy [57-59].

Efficacy

A total of six studies fulfilled the criteria for inclusion in the guidelines [56, 60-64]. Methotrexate monotherapy was investigated in three of these studies, one of which was assigned a grade of evidence of A2 [61], and two of which were assigned a grade of evidence of C [56, 63]. Combination therapy was assessed in the three remaining studies, one of which was assigned a grade of evidence of B [60], and two of which were assigned a grade of evidence of C [62, 64]. For monotherapy with methotrexate, this translates into an overall level of evidence of 2.

Most studies on the efficacy of methotrexate were performed during the 1960s and 1970s and frequently did not comply with the methodological standards applied today. Clinical experience with methotrexate is far greater than the limited number of included studies might imply.

In the study by Heydendael with 88 patients (grade of evidence A2), monotherapy with methotrexate was compared to monotherapy with ciclosporin. Using a PASI reduction of 90%

as an outcome measure, the study showed that a higher percentage of patients treated with methotrexate achieved total remission (40%) compared to those taking ciclosporin (33%). For a PASI reduction of 75%, however, ciclosporin demonstrated higher efficacy, with 71% of patients achieving partial remission compared to 60% of patients taking methotrexate [61].

Two small studies by Nyfors and Weinstein from the 1970s give little or no detailed data on the time at which the success of treatment was assessed, and neither study used PASI scores. Nyfors showed a clearing of the skin lesions in 62%, and a reduction of at least 50%, in 20% of 50 patients [63]. Weinstein showed an improvement of at least 75% of skin lesions in 77% of 25 patients [56].

Asawanonda examined the use of methotrexate in addition to UVB phototherapy in 24 patients. With methotrexate in addition to standard narrowband UVB, a PASI reduction of 90% was achieved in 91% of patients after 24 weeks, whereas only 38% of patients achieved the same treatment success with UVB monotherapy [60]. Similar synergistic effects were shown by Paul, with complete clearance of lesions in all 26 patients after 16 weeks using methotrexate and UVB phototherapy, as well as by Morison, with total remission in 28 out of 30 patients treated with methotrexate and PUVA over a mean duration of 5.7 weeks [62, 64].

Adverse drug reactions/safety

Usually, the prevalence and severity of side effects depend on the dose and dosing regimen. If adverse events occur, the dose should be decreased or the therapy discontinued, and reconstructive measures instituted, such as supplementation with folic acid. The two most important adverse drug reactions associated with methotrexate therapy are myelosuppression and hepatotoxicity.

The risk of liver fibrosis or cirrhosis is slight if appropriate screening and monitoring procedures are adopted. Alcohol consumption, obesity, hepatitis, and diabetes mellitus, which are very common in patients with severe psoriasis, increase the risk of hepatotoxicity. The risk for hepatotoxicity seems to increase further after a cumulative dosage of > 3g Methotrexate and /or > 100g/week of alcohol consumption [65, 66]. The assessment of the risk of severe liver damage from methotrexate and the recommendations for screening differ. They range from regular serum liver function tests to liver biopsy according to certain time and dose intervals. Liver biopsy has been the standard for detecting liver fibrosis and cirrhosis. Today, however, most European countries have adopted the alternative of assaying procollagen type III N-terminal peptide (PIIINP) in serum. Where possible, PIIINP

measurement should be performed prior to starting methotrexate and thereafter every three months. Patients whose PIIINP levels are consistently normal are very unlikely to have significant liver damage, and liver biopsies may be restricted to the small minority in whom PIIINP levels are repeatedly elevated. Because the risk of serious liver damage in carefully monitored patients receiving once weekly low-dose methotrexate is small, the cost and morbidity of repeated liver biopsy may be difficult to justify when compared with the low yield of significant liver pathology. However, interpreting the individual values of PIIINP is not easy, and active joint involvement, smoking, and other factors may lead to an increase in PIIINP levels. Furthermore, additional factors, such as patient age, disease severity, and the possibility of concomitant medication, must be considered when deciding whether to a) perform a liver biopsy, b) withdraw, or c) continue treatment despite raised PIIINP levels [67-69]. In the future, dynamic liver scintigraphy may represent another option for diagnosing liver fibrosis.

In fact, however, most causes of death due to methotrexate are the result of bone marrow suppression. Informing patients about the early symptoms of pancytopenia (dry cough, nausea, fever, dyspnoea, cyanosis, stomatitis/oral symptoms, and bleeding) may aid early detection.

Hypoalbuminaemia and reduced renal function increase the risk of adverse drug reactions. Special care should be taken when treating geriatric patients, in whom doses should usually be lower and kidney function monitored regularly.

Methotrexate is absolutely contraindicated in pregnancy and breastfeeding, as well as in both men and women attempting conception. The washout period is three months for both sexes.

Table 3: Overview of important side effects

Very frequent	Nausea, malaise, hair loss
Frequent	Elevated transaminases, bone marrow suppression, gastrointestinal ulcers
Occasional	Fever, chills, depression, infections
Rare	Nephrotoxicity, liver fibrosis, and cirrhosis
Very rare	Interstitial pneumonia, alveolitis

Important contraindications/restrictions on use

Absolute contraindications

- Severe infections
- Severe liver disease
- Renal failure
- Conception (men and women)/breastfeeding
- Alcohol abuse
- Bone marrow dysfunction/haematologic changes
- Immunodeficiency
- Acute peptic ulcer
- Significantly reduced lung function

Relative contraindications

– Kidney or liver disorders
– Old age
– Ulcerative colitis
– History of hepatitis
– Lack of compliance
– Active desire to have a child for women of childbearing age and men
– Gastritis
– Diabetes mellitus
– Previous malignancies
– Congestive heart failure

Drug interactions

After absorption, methotrexate binds in part to serum albumin. A number of drugs, including salicylates, sulphonamides, diphenylhydantoin, and some antibiotics (i.e. penicillin, tetracyclines, chloramfenicol, trimethoprime), may decrease this binding, thus raising the risk of methotrexate toxicity. Tubular secretion is inhibited by probenecid, and special care should be taken when using this drug with methotrexate. Some drugs with known kidney or liver toxicity, as well as alcohol, should be avoided. Special care should be paid to patients who use azathioprine or retinoids simultaneously. Some nonsteroidal anti-inflammatory drugs (NSAIDs) may increase methotrexate levels and, consequently, methotrexate toxicity,

especially when methotrexate is administered at high doses. As a result, it is recommended that NSAIDs be administered at different times of day than methotrexate. The question of whether folic acid reduces the efficacy of methotrexate remains controversial. There is some evidence that the combination of methotrexate and folic acid may reduce adverse reactions without affecting efficacy [57-59].

Table 4: List of most important drugs with potential interactions

Drug	Type of interaction
Colchicines, ciclosporin, NSAIDs, penicillin, probenecid, salicylates, sulfonamides	Decreased renal elimination of methotrexate
Chloramphenicol, co-trimoxazole, cytostatic agents, ethanol, NSAIDs, pyrimethamine, sulfonamides	Increased risk of bone marrow and gastrointestinal toxicity
Barbiturates, co-trimoxazole, phenytoin, probenecid, NSAIDs, sulfonamides	Interaction with plasma protein binding
Ethanol, leflunomide, retinoids, tetracyclines	Increased hepatotoxicity

Instructions for use

Necessary measures
<u>Pre-treatment</u> • History and clinical examination • Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • Laboratory parameters (see Table 6, page 23) • Chest X-ray • Contraception in women of child-bearing age (starting after menstruation), and also in men • If abnormalities in liver screening are found, refer patient to specialist for further evaluation <u>During treatment</u>

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Check concomitant medication
- Clinical examination
- Laboratory controls (see Table 6, page 23)
- Contraception in women of child-bearing age, and also in men
- 5 mg folic acid once weekly 24 hours after methotrexate*

Post-treatment

- Women must not become pregnant and men must not conceive when they are taking the drug and for at least three months thereafter

** The evidence for the recommendation is scarse. Therefore some of the voting experts felt that flexibility in the dosing of folic acid is warranted, suggesting dosing of 1-5 mg folic acid per day (seven days a week) or 2.5 mg folic acid once weekly 24 hours after methotrexate.*

Overdose/measures in case of overdose

In methotrexate overdose, clinical manifestations of acute toxicity include myelosuppression, mucosal ulceration (particularly of the oral mucosa), and, rarely, cutaneous necrolysis. The last of these complications is also occasionally seen in patients with very active, extensive psoriasis when the dose of methotrexate is increased too rapidly. Relative overdose is usually precipitated by factors that interfere with methotrexate renal excretion or by drug interactions. Folinic acid is a fully reduced folate coenzyme that, after intracellular metabolism, can function in nucleic acid synthesis, thus bypassing the action of methotrexate. As the interval between methotrexate administration and the initiation of folinic acid increases, the efficacy of folinic acid as an antidote to haematological toxicity decreases.

Measures in case of overdose:

- Administer folinic acid (Calcium Leucovorin) immediately at 20 mg (or 10 mg/m^2) intravenously or intramuscularly. Subsequent doses should be given at six-hour intervals either parenterally or orally
- If possible, measure serum levels of methotrexate and adjust doses of folinic acid according to the following schedule:

Table 5: Doses of folinic acid in case of overdose

Serum MTX (M)	Parenteral folinic acid dose given once every six hours (mg)
5×10^{-7}	20
1×10^{-6}	100
2×10^{-6}	200
$>2 \times 10^{-6}$	Increase proportionately

- Measure methotrexate levels every 12 to 24 hours
- Continue to administer folinic acid every six hours until serum methotrexate concentration $<10^{-8}$ M
- If methotrexate levels are not routinely available, the dose of folinic acid should be at least equal to or higher than that of methotrexate, because the two agents compete for transmembrane carrier sites in order to gain access to cells; where folinic acid is given orally, doses need to be multiples of 15 mg. In the absence of methotrexate levels, folinic acid should be continued until the blood count has returned to normal and the mucosae have healed.

Table 6: Lab controls

	Period in weeks/months			
Parameter*	Pre-treatment	After first week	During first two months, 1x every 2 weeks	Thereafter, every 2-3 months
Blood count	x	x	x	x
Liver enzymes	x		x	x
Serum creatinine	x		x	x
Urine sediment	x		x	x
Pregnancy test (urine)	x			
HBV/HCV	x			
Serum albumin**	x		x	x
PIIINP where available	x		Every 3 months***	
Further specific testing may be required according to clinical signs, risks, and exposure.				

* If blood leucocytes <3.0, neutrophils <1.0, thrombocytes <100, or liver enzymes >2x baseline values, decrease the dose or discontinue the medication

** In selected cases (e.g. in cases with suspected hypoalbuminaemia or in patients using other drugs with high binding affinity for serum albumin)

*** Liver biopsy when necessary in selected cases; should be considered, for example, in patients with persistently abnormal PIIINP (>4.2 mcg/l in at least three samples over a 12-month period)

Special considerations

Alcohol consumption, obesity, hepatitis, and diabetes mellitus increase the risk of hepatotoxicity. Special care should be taken when treating geriatric patients, in whom doses should usually be lower and kidney function monitored regularly.

Combination therapy

The effectiveness of methotrexate can be further increased by the combination with UVB or PUVA therapy. In an open-label study by Morison et al (grade of evidence C) investigating the combination of methotrexate/PUVA in 30 patients, the percentage of patients with complete remission was 93% after an average of 5.7 weeks [62]. The specific adverse drug reactions resulting from the combination with phototherapy have not been defined and require long-term follow-up. Only increased phototoxicity has been described as a possible consequence of combined methotrexate/PUVA therapy; this was not observed in the methotrexate/UVB combination study by Paul et al (grade of evidence C) [64]. There is some indication that methotrexate leads to increased phototoxicity with UVB.

Table 7: Possibilities for therapeutic combination

	Recommendation	Comments
Ciclosporin	-	Combination possible, but increased immunosuppression must be considered
Retinoids	-	Increased hepatotoxicity
Fumaric acid esters	-	Increased immunosuppression; case reports of successful combination treatment exist [70]
Biologics	+, +/-	See respective chapters
Phototherapy	+	PUVA or UVB, increased phototoxicity

Summary

Of 11 studies investigating the efficacy of methotrexate monotherapy in psoriasis vulgaris, a total of three fulfilled the criteria for inclusion in the guidelines. After 16 weeks of treatment with methotrexate, approximately 60% of patients displayed a 75% reduction in PASI (level of evidence 2).

Clinical experience with methotrexate is much greater than the documentation of the efficacy and safety of methotrexate therapy in clinical studies. Clinical experience has demonstrated that the efficacy of methotrexate continues to increase with longer treatment. As a result, methotrexate represents, above all, an effective therapeutic option for long-term therapy. Its clinical application is restricted by severe adverse drug reactions, including especially hepatotoxicity, bone marrow suppression, gastrointestinal ulcerations, and very rare, but severe idiosyncratic reactions. However, with precise patient selection, thorough patient information, strict monitoring, use of the lowest effective dose, and the additional administration of folic acid, an acceptable safety profile can also be attained for methotrexate therapy.

Therapeutic recommendations

- Part of the guidelines group believes that methotrexate (15-22.5 mg/week) should be recommended based on many years of clinical experience with this agent and on the included studies; other members believe that methotrexate should only be suggested for the treatment of psoriasis vulgaris because of the limited evidence available (only one A2 trial) in the studies.
- Methotrexate is, as a result of its slow onset of action, less desirable for short-term induction therapy than for long-term therapy.

3.2 Ciclosporin

Dubertret/Griffiths

Introduction/general information

Ciclosporin (originally described as ciclosporin A) is a neutral, strongly hydrophobic, cyclic undecapeptide (hence the prefix "cyclo" or "ciclo") of 11 amino acids that was first detected in the early 1970s in the spores (hence the suffix "sporin") of the fungus *Tolypocladium inflatum Gams*. It was first introduced into transplantation medicine under the trade name Sandimmune®. Based on the experiences obtained in that field, the effects of ciclosporin were also investigated in other immune-mediated diseases [71]. Ciclosporin has been used to treat psoriasis vulgaris since the early 1990s and was approved for this indication in 1993. The absorption of ciclosporin in the original preparation, Sandimmune®, was slow, incomplete, hard to calculate, and dependent on intestinal bile acid levels. Today, the microemulsion formulation (Sandimmune Optoral® or Neoral®) is usually employed. This formulation demonstrates more consistent absorption that is less dependent on bile production; as a result, the dose correlates better with blood levels of ciclosporin [72]. In isolated cases, Sandimmune® solution may still be used.

Ciclosporin is indicated in patients with the most resistant forms of psoriasis, especially with plaque-type disease. In the age of biologics, ciclosporin is classified as a traditional systemic therapy. In practice, selecting a suitable therapy should be based on a variety of parameters, including age, sex, disease course and activity, previous therapies, concomitant diseases and medications, burden of the disease, and the presence or absence of psoriatic arthritis [73]. Ciclosporin is used as a short-term therapy for two to four months; courses of treatment can be repeated at intervals. Less frequently, it is used for continuous long-term therapy over a period of one to two years.

Table 8: Tabular summary

Ciclosporin	
Approval for psoriasis	1993
Recommended control parameters	Interview/examination as detailed in the instructions for use table, pages 38-39 *Laboratory:* Creatinine, uric acid, liver enzymes, bilirubin, alkaline phosphatase, potassium, magnesium,

	urinalysis, complete blood count, cholesterol/triglycerides, pregnancy test
Recommended initial dosage	2.5-3 (max. 5) mg/kg daily (4-6 weeks)
Recommended maintenance dosage	**Interval therapy** (over 8-16 weeks) with dose reduction at the end of induction therapy (e.g. 0.5 mg/kg every 14 days) or **Continuous long-term therapy** Dose reduction every two weeks to a maintenance dosage of 0.5-3 mg/kg/day. In case of relapse dosage increase (according to [74]) Maximum total duration of therapy: 2 years
Clinically significant response expected after	4 weeks
Response rate	Dose-dependent, after 8-16 weeks with 3 mg/kg daily; PASI 75 in approximately 50% after 8 weeks
Absolute contraindications	Impaired renal function; uncontrolled hypertension; uncontrolled infections; malignant disease (current or previous, in particular haematologic diseases or cutaneous malignancies, with the exception of basal cell carcinoma)
Important side effects	Renal failure, hypertension, liver failure, nausea, anorexia, vomiting, diarrhoea, hypertrichosis, gingival hyperplasia, tremor, malaise, paresthesias
Important drug interactions	Many different interactions; see text and product information sheet
Special issues	Increased risk of lymphoproliferative disease in transplant patients. Increased risk of squamous cell carcinoma in psoriasis patients following ecessive photochemotherapy

Mechanism of action

Pharmacokinetics

Ciclosporin has a molecular weight of 1.2 kDa. Topically applied, ciclosporin does not penetrate intact skin, but intralesional ciclosporin has a favourable effect on psoriatic plaques [75, 76]. The highest level of ciclosporin is measured approximately two hours after oral administration of the micro-emulsion formulation. Individual variability is relatively large, but less than with the older formulations. The availability of ciclosporin (peak concentration, clearance of oral ciclosporin) depends primarily on the activity of the intestinal transporter

protein p-glycoprotein (P-gp) and metabolism by CYP3A4 and CYP3A5 isoenzymes. The expression of CYP3A, P-gp, and CYP3A isoenzymes is subject to genetic polymorphism, which may affect individual dosing requirements. It is essential to know which drugs are co-administered with ciclosporin because interactions at the level of CYP3A isoenzymes or P-gp may affect ciclosporin plasma levels in both directions, resulting in increased toxicity or a decreased immunosuppressive effect. With the use of the ciclosporin generics, an average of 20% lower bioavailability can be expected, which means that efficacy may be unsatisfactory in isolated cases.

Pharmacodynamics

One important mechanism in the activation of T cells is the nuclear translocation of factors that cause an increased expression of pro-inflammatory messenger substances. This group of transcription factors includes the nuclear factors of activated T cells (NFATs). After activation via the T-cell receptor, the enzyme phospholipase C releases inositol triphosphate (IP3) from the membrane receptor phospholipids, resulting in an increase in the concentration of intracellular calcium. After binding to calmodulin, calcium activates a calcineurin phosphatase, which catalyzes dephosphorylation of NFAT, enabling translocation of NFAT into the cell nucleus and there, together with other transcription factors, binds to the regulatory segments of the various target genes and induces their transcription. Ciclosporin binds to cyclophilin, a cytoplasmic immunophilin; the ciclosporin-immunophilin complex inhibits phosphatase activity of the calcium-calmodulin-calcineurin complex and thus the translocation of NFAT and subsequent NFAT-dependent cytokine production. Because it inhibits production of important immunological messenger substances, especially in T cells, ciclosporin is considered to be a selective immunosuppressant. Its effect is reversible, and it has neither myelotoxic nor mutagenic properties [77].

Dosing regimen

The initial dosage of ciclosporin is generally 2.5 to 3 mg/kg daily, although it should be noted that a rigidly weight-oriented dosage of 1.25 to 5 mg/kg daily could not be shown to be superior to a body-weight-independent dosage of 100 to 300 mg daily in a comparative study [78]. The daily dose is always administered in two divided doses, i.e. in the morning and evening. Patients in whom a rapid effect is desired because of the severity of psoriasis may also be treated with an initial dose of 5 mg/kg daily. Although the higher dose results in a faster and more complete clinical response, it is associated with a higher rate of adverse reactions.

Clinical improvement of psoriasis occurs after approximately four weeks, and maximum response is seen after about 8 to 16 weeks. If a patient does not respond satisfactorily to initial therapy over four to six weeks with the lower dose (2.5 to 3 mg/kg daily), the dose can be increased to 5 mg/kg daily if his or her laboratory parameters are satisfactory. If response is still unsatisfactory after an additional four weeks, then ciclosporin should be discontinued.

Short-term therapy

In short-term therapy (i.e. induction therapy), the patient is treated until an adequate response is achieved, which generally requires 10 to 16 weeks. Subsequently, ciclosporin is discontinued. Some studies have indicated that the relapse rate (defined as a decrease of 50% in the improvement initially achieved with therapy) is higher and the period until relapse is shorter if ciclosporin is discontinued abruptly rather than with a slowly tapered reduction of the dose [79, 80]. "Fade-out regimens" include a reduction of 1 mg/kg every week over four weeks, or a reduction of 0.5 to 1 mg/kg every two weeks. With the former, slow-reduction regimen in a study with 30 patients after an initial therapy of 12 weeks, a median time to relapse of 119.5 days was observed [79].

Long-term therapy

Long-term therapy (i.e. maintenance therapy) of psoriasis with ciclosporin should be the exception rather than the rule and should be prescribed only after other therapeutic options have been considered. This is because of possible adverse effects, including an increased risk of developing cutaneous malignancies (especially in patients with high cumulative doses of PUVA [> 1000 J/cm^2]), and because of reports from corresponding case studies of an elevated risk of lymphoma. In one two-year study investigating the intermittent administration of ciclosporin following relapse after the initial induction phase, the mean time in which patients were treated with ciclosporin was 43%, and the mean time in which patients were in remission was 60% [79].

In a 9 to 12 months' study comparing an intermittent regimen to continuous therapy with low doses of ciclosporin, a lower relapse rate was demonstrated in the continuous therapy group. Therfore the following dosing regimen was used: initial treatment with 3.0-5.0 mg/kg/day, after remission (improvement in PASI score) every two weeks decrease to a maintenance dosage of 0.5-3.0 mg/kg/day. In case of relapse the dosage was increased again [74].

Efficacy

A total of 17 studies fulfilled the criteria for inclusion in the guidelines [61, 72, 78, 80-93]; Ciclosporin monotherapy was investigated in 15 of these studies, two of which were assigned a grade of evidence of A2 [72, 82], 10 with a grade of evidence of B [61, 78, 80, 81, 83, 85, 89-91, 93], and three with a grade of evidence of C [84, 87, 88]. This results in a level of evidence of 1. These studies investigated both Sandimmune® and Sandimmune Optoral (Neoral®). The majority of included studies demonstrated a clinically relevant response four to six weeks after the initiation of therapy. In one study by Ellis et al (grade of evidence A2) with 85 patients, complete remission ("cleared" or "extensive clearing") was observed after eight weeks in 65% of the patients treated with 5 mg/kg daily and in 36% of the patients treated with 3 mg/kg daily [82]. In a study by Koo et al (grade of evidence A2) with 309 patients, after eight weeks 51.1% of the patients treated with 2.5 to 5 mg/kg daily Neoral® and 87.3% after 16 weeks had an at least 75% reduction in PASI score [72]. In the 10 studies assigned a grade of evidence of B, a total of 1134 patients received, for the most part, doses of 2.5 to 5 mg/kg daily with an adjustment regimen (possibility of an increase until remission, followed by dose reduction) for a period of 12 to 24 weeks [61, 78, 80, 81, 83, 85, 89-91, 93]. In their study of 12 patients, Engst and Huber (grade of evidence B) observed complete remission in 33.3% and partial remission in 50% of patients after four weeks with 5 mg/kg daily [83]. In the large study by Laburte et al (grade of evidence B) with 251 patients, partial remission was observed after 12 weeks in 47.9% of the patients treated continually with 2.5 mg/kg daily and in 88.6% of the patients treated continually with 5 mg/kg daily [89]. In the other studies, complete remission was observed in 20% to 88% of patients after 8 to 16 weeks, and partial remissions in 30% to 97% of patients. In a recent comparative study by Heydendael et al (grade of evidence B) with 15 to 22.5 mg methotrexate weekly in a total of 88 patients, the ciclosporin patient group treated with 3 to 5 mg/kg daily showed complete remission in 33% of cases (methotrexate: 40%) and partial remission in 71% of cases (methotrexate: 60%) [61] after 16 weeks. However, the average initial PASI score of 14 was significantly below the corresponding score seen in most of the other studies (generally >20). In an eight-arm comparative study with sirolimus by Reitamo et al (grade of evidence B), partial remission was observed after eight weeks in 5 of 19 (26%) patients treated with 1.25 mg/kg daily and in 10 of 15 (67%) patients treated with 5 mg/kg daily [93]. In two older studies by Finzi et al (grade of evidence C) and Higgins et al (grade of evidence C), a total of 30 patients were treated with ciclosporin 3 to 5 mg/kg daily over 9 to 12 weeks [84, 88]. In the open-label study by Finzi et al, partial remission was observed after 3 weeks in 92.3% of 13 patients [84]. In a study by Grossman et al (grade of evidence C),

4 of 34 (12%) patients treated with 2 mg/kg daily achieved complete remission after six weeks [87]. In the 17 included studies on induction therapy, information was collected on relapse rates several months after therapy in five studies, showing relapse rates of 50% to 60% after six months and 70% after eight months [78, 84, 85, 88, 90]. There were no reports of marked tachyphylaxis or rebound phenomena in the clinical studies on induction therapy. In about one third of the patients, a clinical deterioration can be expected three to four weeks after the end of induction therapy, depending on whether the therapy is reduced in steps or abruptly. On average, only about 50% of the initial clinical improvement is present three months after the end of therapy. In one long-term study with intermittent administration of ciclosporin over two years, there was an increasingly shorter median period until the time of relapse (i.e. of 116 days after the first treatment cycle to 40 days after the seventh cycle of treatment) [79].

Adverse drug reactions/safety

In the included studies, adverse effects for ciclosporin were reported primarily for short-term (i.e. induction) therapy. When several doses of ciclosporin were studied, the rate of adverse effects generally demonstrated a clear dose dependency [82]. The most frequently reported adverse effects included:

Kidneys/blood pressure

- Increases in serum creatinine (average 5% to 30% for entire group); in up to 20% of patients, increases in creatinine of more than 30%
- Reduced creatinine clearance (average up to 20%)
- Increased blood urea nitrogen in 50% of patients; increased uric acid in 5% of patients
- Decreased Mg (average 5% to 15%)
- Arterial hypertension in 2% to 15% of patients

Liver/gastrointestinal tract

- Gastrointestinal symptoms (nausea, diarrhoea, flatulence in 10% to 30% of patients)
- Increased bilirubin in 10% to 80% of patients
- Increased transglutaminases in up to 30% of patients
- Gingival hyperplasia in up to 15% of patients

Other

- Paresthesias in up to 40% of patients
- Muscle aches in 10% to 40% of patients

- Headache in 10% to 30% of patients
- Tremor in 2% to 20% of patients
- Hypertrichosis in <5% of patients

Adverse effects have also been reported in long-term studies (i.e. up to two years). In one study with 251 randomized patients receiving ciclosporin 2.5 mg or 5 mg/kg daily for up to 21 months, adverse events were observed in 54% of the patients taking the drug; 8% of these adverse events were classified as severe [89]. In about every fifth patient (18%), therapy was discontinued as a result of adverse events. Therapy was discontinued as a result of an increase in serum creatinine of >30% in 24 patients (10%) and as a result of arterial hypertension in 6% of patients. While the latter was not dose dependent, the former was in a total of 46% of patients in this long-term study (compared with up to 20% in the short-term studies) [79].

As shown in one long-term study with 220 patients, the incidence of side effects is correlated with dose, duration of treatment, age, diastolic blood pressure, and serum creatinine [94].

Table 9: Overview of important side effects

very frequent	None
Frequent	Renal failure (dose-dependent); danger of irreversible renal damage (long-term therapy); hypertension; gingival hyperplasia; reversible hepatogastric complaints (dose dependent); tremor; weariness; headache; burning sensation in hands and feet; reversible elevated blood lipids (especially in combination with corticosteroids); hypertrichosis
Occasional	Seizures, gastrointestinal ulcerations, weight gain, hyperglycaemia, hyperuricaemia, hyperkalaemia, hypomagnesaemia, acne, anaemia
Rare	Ischemic heart disease, pancreatitis, motor polyneuropathy, impaired vision, defective hearing, central ataxia, myopathy, erythema, itching, leucopoenia, thrombocytopenia
very rare	Microangiopathic haemolytic anaemia, haemolytic uremic syndrome, colitis (isolated cases), papillary oedema (isolated cases), idiopathic intracranial hypertension (isolated cases)

Malignancies

As with other immunosuppressive therapies, Ciclosporin carries an increased risk of developing lymphoproliferative disorders and other malignant tumours, especially of the skin. The incidence of malignancies appears to be dependent primarily on the degree and duration of immunosuppression and on other preceding or concomitant therapies, such as photochemotherapy or methotrexate. Patients must be monitored especially carefully

following long-term therapy with ciclosporin. An increased risk of skin cancer, especially squamous cell carcinomas, has been observed in patients with psoriasis vulgaris who have received long-term photochemotherapy (especially high cumulative doses of PUVA, >1000 J/cm2). In one study of patients who had previously received PUVA, the risk of squamous cell carcinoma was seven times greater after first ciclosporin use than in the previous 5 years (i.e. prior to ciclosporin treatment) after adjusting for PUVA and methotrexate exposure [95]. For the total cohort any use of ciclosporin was associated with a three-fold increase, i.e. comparable to that for at least 200 PUVA treatments. In another cohort study over five years (average duration of ciclosporin treatment 1.9 years), the incidence of malignancies was twice as high as in the general population [96]. This was attributable to a six-fold greater risk of skin cancer, the majority of cases being squamous cell carcinomas. Significant effects on the incidence of non-melanoma skin cancers were demonstrated in these studies based on duration of therapy with ciclosporin and previous therapy with PUVA, methotrexate, or other immunosuppressive agents. Because squamous cell carcinomas can be difficult to diagnose in active psoriasis, a biopsy should be performed if there is any suspicion. There are case reports where therapy with acitretin demonstrated a beneficial effect in psoriasis patients with multiple squamous cell carcinomas as a consequence of immunosuppressive therapy, for example with ciclosporin [97, 98]. In some psoriasis patients treated with ciclosporin, benign lymphoproliferative changes, as well as B- and T-cell lymphomas, occurred but receded when the drug was immediately discontinued. In the literature there are at least 20 single case publications on malignancies in ciclosporin-treated patients with psoriasis vulgaris. Among these there are at least seven cases with nodal or cutaneous lymphomas and several cases with HPV-associated carcinoma.

Infections

As with other immunosuppressive therapies, ciclosporin may increase the general risk of various bacterial, parasitic, viral, and fungal infections, as well as the risk of infections with opportunistic pathogens. As a rule, however, this increased risk of infections plays only a minor role when treating psoriasis vulgaris with ciclosporin. Infections deserve special attention as possible trigger factors for relapse. Patients in whom an infection-triggered exacerbation of psoriasis vulgaris is probable should first be treated with appropriate therapy for the infection, followed by a re-examination of the indication for ciclosporin. An increased tendency to infection has been observed in patients with psoriatic arthritis, who under certain circumstances are treated with various immunosuppressive agents in addition to ciclosporin.

Pregnancy/breastfeeding

From the limited experience available on the safety of administering ciclosporin to pregnant women, there is no indication of teratogenicity. Ciclosporin is not teratogenic in test animals. Initial experiences with recipients of solid organ transplants indicate that ciclosporin increases the probability of pregnancy-specific complications, such as preclampsia and premature birth with lower birth weight. Patients of childbearing age with psoriasis should receive ciclosporin only after a negative pregnancy test and while employing a reliable form of contraception. Ciclosporin can reduce the efficacy of progesterone-containing contraceptives. Nevertheless, there is evidence that ciclosporin has no influence on pregnancy if taken at the beginning of pregnancy. In patients with psoriasis vulgaris in whom a pregnancy occurs while taking ciclosporin, the drug should be stopped and a renewed risk-benefit analysis should be performed together with the patient. If necessary, ciclosporin might be given again with a careful follow up. Ciclosporin and alcohol (the capsules contain 12.7% alcohol) enter into breast milk. For this reason, mothers should not breastfeed when undergoing treatment with ciclosporin.

Ciclosporin in elderly persons

There is only limited experience available on the use of ciclosporin in elderly persons. There are no specific problems when ciclosporin is used according to the recommendations. The risk of developing renal failure after the age of 50 increases greatly under therapy with ciclosporin. For this reason, laboratory monitoring should be stricter in this age group. The presence/occurrence of (UV-related) skin tumours should be given special attention.

Measures in case of adverse drug effects

The adverse drug effects of ciclosporin therapy are generally dose-dependent and respond to dose reduction. Special methods/measures are recommended for some of the adverse effects occurring with ciclosporin. With an increase in serum creatinine of 30% compared to the baseline mean value, an initial check of fluid intake should be performed. If serum creatinine increases by 30% to 50% (even if within normal limits), a reduction in the dose of ciclosporin of at least 25% and another check within 30 days is recommended. If an increase in creatinine of 30% is still present, ciclosporin should be discontinued. If a 50% increase of serum creatinine occurs, the ciclosporin dose should be reduced by at least 50%. In these cases, patients should be re-examined within 30 days and, if creatinine is still 30% above baseline, ciclosporin should be discontinued. If hypertension develops (systolic 160 mmHg or diastolic 90 mmHg in two consecutive measurements), antihypertensive therapy should be initiated or

an existing antihypertensive therapy intensified. Appropriate agents include calcium channel blockers, such as amlodipine (5to 10 mg daily), nifedipine (cave: gingival hyperplasia) or isradipine (2.5 to 5 mg daily). However, calcium antagonists themselves may increase ciclosporin blood levels. This is the case for diltiazem, nicardipine, and verapamil. With the use of beta-blockers there might be the risk of triggering psoriasis. Therapy with ACE inhibitors or ATII receptor antagonists increases the risk of a hyperkalaemia. If, despite calcium channel blockers, a patient's blood pressure remains above the aforementioned limits, the ciclosporin dosage should be reduced by 25%. If this does not result in a normalization of blood pressure, therapy with ciclosporin should be discontinued. Hypomagnesaemia should be treated with magnesium supplements (begin with 200 mg magnesium daily), which may be increased if needed. If the tolerance and efficacy of ciclosporin are otherwise good and there are no neurological disturbances associated with the decreased magnesium levels, no further measures are required. With hyperkalaemia, a low potassium diet and sufficient fluid intake (2-3 L daily) should be recommended to the patient. If the response is not satisfactory, the ciclosporin dose should be reduced by 25%. The possible occurrence of arrhythmia with hyperkalaemia and the possible need for acute intervention should be kept in mind. Changes in serum potassium and magnesium levels have been observed in particular in patients with pronounced renal failure. With hyperuricaemia, a low purine diet and sufficient volume of liquids is recommended (2-3 L daily). If there is a lack of improvement and the situation appears to be threatening for the patient, the dosage should be reduced by 25%. If no improvement is achieved, the medication should be discontinued. With regard to co-medication with allopurinol, please refer to the subchapter on drug interactions.

With an increase in transaminases or total bilirubin to more than twice the normal value, a reduction in the dose of ciclosporin by 25% and subsequent reassessment within 30 days is recommended. If the laboratory values continue to deviate, ciclosporin should be discontinued. With an increase in blood lipids (fasting values for cholesterol and/or triglycerides), a low-cholesterol, low-fat diet should be recommended. If no improvement is achieved, a reduction in dose or discontinuation of therapy with ciclosporin should be considered, depending on the degree of hyperlipidaemia and the patient's risk profile. Isolated cases of serious, but reversible, impairment of renal function with a corresponding increase of serum creatinine has been observed in organ-transplant patients with the simultaneous use of fibrate-containing drugs (bezafibrate, fenofibrate). Ciclosporin may reduce the clearance of some HMG-CoA reductase inhibitors (lovastatin); as a result, their plasma levels and toxicity may be increased (muscle aches, myasthenia, myositis, and rhabdomyolysis). A

corresponding warning in the expert information recommends close monitoring of patients in whom ciclosporin and statins are used together (determination of the serum creatinine phosphokinase values) so as to detect myopathy at an early stage followed by a dosage reduction or, if needed, discontinuation of the statin. Simultaneous use of ezetimibe (Ezetrol®) is possible; however, interactions have been described (increase of the mean area under the curve (AUC) of total ezetimibe). If gingival hyperplasia develops, optimal dental hygiene must be insured. Depending on the degree and progress of the findings, a dose reduction or discontinuation of ciclosporin is recommended.

Important contraindications/restrictions on use

Absolute contraindications

- Impaired renal function
- Insufficiently controlled arterial hypertension
- Severe infectious disease
- History of malignancy (possible exceptions: treated basal cell carcinoma, history of squamous carcinoma in situ)
- Current malignancy
- Simultaneous PUVA therapy

Relative contraindications

– Previous potential carcinogenic therapies (e.g. arsenic, PUVA >1000 J/cm2)
– Psoriasis triggered by severe infection or drugs (beta-blockers, lithium, anti-malarial drugs)
– Significant hepatic diseases
– Hyperuricaemia
– Hyperkalaemia
– Simultaneous therapy with nephrotoxic drugs (see drug interactions)
– Simultaneous phototherapy (SUP, except PUVA, see above)
– Simultaneous use of other systemic immunosuppressive agents
– Simultaneous use of systemic retinoids or therapy with retinoids in the last four weeks prior to planned onset of therapy with ciclosporin
– Drug or alcohol-related diseases
– Long-term previous treatment with methotrexate
– Pregnancy/breastfeeding
– Vaccination with live vaccines

– Epilepsy
– Current treatment with castor oil preparations

Drug interactions

The availability of ciclosporin depends primarily on the activity of two molecules – the hepatic enzyme cytochrome P450-3A4 (CYP3A4), which is involved in its metabolism, and the intestinal P-glycoprotein, an ATP-dependent transporter protein that transports various drugs, among them ciclosporin, from the enterocytes back into the intestinal lumen. The activities of these molecules may both vary for genetic reasons and be influenced by drugs and herbal substances [99]. Above all, modulators and substrates of CYP3A are relevant for therapeutic practice. The calcium-antagonist diltiazem, the antimycotics ketoconazole and itraconazole, the macrolide antibiotics (with the exception of azithromycin), and grapefruit juice are strong inhibitors of the CYP3A with the risk of ciclosporin overdosing, while the phytopharmaceutical agent St John's wort is a CYP3A inductor, with the risk of sub-therapeutic ciclosporin levels. Because a worsening of myopathy due to the simultaneous intake of HMG-CoA reductase inhibitors (statins) is possible, the risks of concomitant statin therapy should be weighed carefully. In addition, interactions that could exacerbate adverse drug reactions such as nephrotoxicity must be considered.

Ciclosporin levels are increased (CYP3A inhibition) by:

Calcium antagonists (diltiazem, nicardipine, nifedipine, verapamil, mibefradil), amiodarone, macrolide antibiotics (erythromycin, clarithromycin, josamycin, posinomycin, pristinamycin), doxycycline, gentamicin, tobramycin, ticarcillin, quinolones (such as ciprofloxacin), ketoconazole and – less pronounced – fluconazole and itraconazole, oral contraceptives, androgenic steroids (norethisterone, levonorgestrel, methyl testosterone, ethinyl estradiol), danazol, allopurinol, bromocriptine, methylprednisolone (high doses), ranitidine, cimetidine, metoclopramide, propafenone, protease inhibitors (e.g. saquinavir), acetazolamide, amikacin, statins (above all atorvastin and simvastatin), cholic acids and derivatives (ursodeoxycholic acids), grapefruit juice.

Ciclosporin levels (CYP3A induction) are increased by:

Carbamazepine, phenytoin, barbiturates, metamizole, rifampicin, octreotide, ticlopidine, nafcillin, probucol, troglitazone, intravenously administered sulfadimidine and trimethoprim, St John's wort.

Possible reinforcement of nephrotoxic adverse drug reactions through:

Aminoglycoside (e.g. gentamicin, tobramycin), amphotericin B, trimethoprim and sulfamethoxazole, vancomycin, ciprofloxacin, aciclovir, melphalan, NSAIDs (diclofenac, naproxen, sulindac). It is recommended that the creatinine values be determined more frequently with these preparations; if necessary, reduce the dosage of the comedication. A considerable (reversible) impairment of renal function is possible with fibrates (bezafibrate and fenofibrate). On the other hand, during ciclosporin therapy, an increased plasma level of some drugs occurs as a result of reduced clearance. This is true for digoxin, colchicine, prednisolone, some HMG- CoA reductase inhibitors (e.g. lovastatin), and diclofenac. The cause is probably a reduced first-pass effect (increased danger of renal damage).

Other interactions

Increased risk of a gingival hyperplasia with the simultaneous intake of nifedipine; increased immunosuppression/tumour risk with simultaneous treatment with other immunosuppressive agents or tumour-inducing substances; vaccination may be less effective; ciclosporin may reduce the effect of progesterone-containing contraceptives; with high doses of prednisone, prednisolone, or methylprednisolone, the risk of cerebral convulsions is increased. As a result of the disulfiram-like effect that has been observed following the administration of N-methyl-thiotetrazole cephalosporin (cefotetan), the simultaneous administration of ciclosporin (alcohol-containing drug) should be performed with care.

Instructions for use

Necessary measures
<u>Pre-treatment</u> • Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/ Skindex-29 or -17) • History and clinical examination should focus on previous and concomitant diseases (e.g. severe infections; malignancies, including cutaneous malignancies; renal and liver diseases) and concomitant medication (see Drug interactions) • Measurement of the blood pressure on two separate occasions • Laboratory controls (see Table 10, page 40) • Reliable contraception (cave: reduced efficacy of progesterone-containing contraceptives)

- Regular gynaecologic screening according to national guidelines
- Consultation on vaccination; susceptibility to infections (take infections seriously, seek medical attention promptly); drug interactions (inform other treating physicians about therapy); avoidance of excessive sun exposure; use of sunscreens

During treatment

In uncomplicated long-term therapy with low dose ciclosporin (2.5 to 3 mg/kg daily), follow-up intervals may be extended to two months or more. Shorter intervals may be needed in patients with risk factors, dose increases, or those who must take concomitant medications that are likely to contribute to ADRs. In selected patients with intermittent and short-term treatment, less strict monitoring (regular checking of blood pressure and creatinine level) may be sufficient.

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Clinical examination should focus on status of skin and mucous membranes (increase of body hair, gingival changes), signs of infections, gastrointestinal or neurological symptoms
- Repeat recommendation for sun avoidance and sun protection
- Check of concomitant medication
- Measurement of blood pressure
- Laboratory controls (see Table 10, page 40)
- Reliable contraception
- Regular gynaecologic screening according to national guidelines*
- If creatinine is significantly elevated and/or patient on therapy for >1 year, perform creatinine clearance (or creatinine- EDTA clearance where available).
- Determination of the ciclosporin level is recommended in individual cases

Post-treatment

- After discontinuation of ciclosporin, patients should be followed up for skin cancer, especially in case of extensive prior therapeutic or natural UV exposure.

** A consensus (defined as agreement by at least 75% of the voting experts) could not be reached for this point. This percentage of positive votes in this case was 58%.*

Overdose/measures in case of overdose

If overdose is suspected, the following approach is recommended:

- Determine ciclosporin serum level
- Interrupt ciclosporin
- Determine vital parameters, liver, renal values, electrolytes
- If needed, introduce additional measures (including consultation with other specialists)

Measuring ciclosporin levels

When treating patients with dermatologic diseases, it is generally not necessary to measure ciclosporin blood levels. An assay may be performed to obtain information about drug intake (compliance) (in case of a discrepancy between (higher) doses and clinical response or discrepancy between (lower) doses and occurrence of ADRs) or with the simultaneous intake of drugs that might influence ciclosporin levels.

Table 10: Lab controls during treatment with ciclosporin

	Period in weeks					
Diagnostics	Pre-treatment	2	4	8	12	16
Full blood count*	x	x	x	x	x	x
Liver values**	x	x	x	x	x	x
Electrolytes***	x	x	x	x	x	x
Serum creatinine	x	x	x	x	x	x
Urine status and sediment	x		x			x
Uric acid	x		x	x	x	x
Pregnancy test (urine)	x					
Cholesterol, triglycerides	x****			x		x
Magnesium*****	x			x		x
Further specific testing may be required according to clinical signs, risk, and exposure.						

* Erythrocytes, leucocytes, platelets

** Transaminases, AP, gGT, bilirubin

*** Sodium, potassium

**** Recommended two weeks before and on the day of treatment initiation (fasting)

***** Only with indication (muscle cramps)

Special considerations

- The following special warnings are listed in the expert information:
  - The capsules contain alcohol (12.7 vol. % alcohol; intake of 100 mg capsules is the equivalent of 0.1 g alcohol). Thus, there is a potential health risk for patients with liver disease, epilepsy or brain damage, alcoholics, pregnant women and children, among others.
  - There is the potential for multiple drug reactions, especially with statins (increased risk of myopathy). Compared to other anti-psoriatic systemic agents, the risk of drug interactions and adverse reactions should be given special consideration.
  - There have been isolated reports of possible intracranial pressure increase. If idiopathic intracranial hypertension (pseudotumor cerebri) is diagnosed along with the corresponding neurological symptoms, ciclosporin should be discontinued because a permanent impairment of vision may result.
- An annual measurement of glomerular filtration rate on cumulative treatment is the most accurate method to assess renal tolerance under long-term or repeated treatments [100, 101].
- Magnesium supplementation appears to protect the kidneys, preventing chronic ciclosporin nephrotoxicity by adjusting nitric oxide synthase activity [102].

Combination therapy

Table 11: Possibilities for therapeutic combination

	Recommendation	Comments
Phototherapy	-	Increased risk of SCC reported for PUVA
Methotrexate	-	Increased immunosuppression but combination is possible
Retinoids	-	No evidence of increased efficacy
Fumaric acid esters	-	Case reports of successful combination treatment exist [70]
Biologics	Differs depending on biologic agent	See relevant chapters

Special consideration when switching therapy

When switching between different preparations of ciclosporin produced by various manufacturers, potential differences in the bioavailability should be considered and the dose possibly adjusted. There are no fixed rules for rotation therapy with ciclosporin, although it is best to use ciclosporin after rather than before PUVA. Ciclosporin can be used after systemic therapy with retinoids, but only after an interval of four weeks. Fumaric acid esters and ciclosporin are generally not given together. A switch to therapy with fumaric acid esters presents the problem of the long onset of action with these preparations and the danger of an exacerbation. If there is an inadequate response to ciclosporin, a switch to a biologic with a period of concomitant administration may be reasonable, even considering possible synergistic toxicity (infections, hepatotoxicity).

Summary

Of 65 studies evaluated with respect to the efficacy of ciclosporin monotherapy in psoriasis, 15 fulfilled the criteria for inclusion in the guidelines. Ciclosporin demonstrated high efficacy among adults in these clinical studies. After 12-16 weeks of treatment, approximately 50% of patients achieved a PASI 75 in the included A2 studies (level of evidence 1). Ciclosporin is primarily suited for induction therapy; in long-term therapy, the risks and benefits for each individual patient must be weighed carefully due to adverse drug reactions, especially nephrotoxicity and increases in blood pressure, as well as a potentially increased risk of malignancies.

When using ciclosporin, a variety of drug reactions need to be considered that can either lead to a change in the availability of ciclosporin or concomitant medications, or to an increased risk of adverse drug reactions.

As a result of its long-term use for various indications, including psoriasis vulgaris, there is extensive data available for this agent, also with regard to its safety during long-term therapy. Ciclosporin represents an effective systemic therapy for moderate to severe psoriasis vulgaris.

Therapeutic recommendations

- Ciclosporin is suggested primarily for induction therapy in adults with moderate to severe psoriasis vulgaris who cannot be sufficiently treated with topical therapy and/or phototherapy.
- Ciclosporin can be considered for long-term therapy (up to two years) in individual cases, but patients should be monitored closely for signs of increasing toxicity, especially for decreases in renal function or the efficacy of treatment.

3.3 Retinoids

van de Kerkhof/Girolomoni

Introduction/general information

For decades, topical and oral retinoids have been used as antipsoriatic treatments. Etretinate (Tigason®), acitretin (Neotigason®), and isotretinoin (Roaccutane®) have been used in the treatment of psoriasis.

The first study with etretinate was published in 1975, the first with acitretin in 1984. Both retinoids have been approved for the treatment of psoriasis, in contrast to isotretinoin, which was not approved for this indication as it is less effective than etretinate [103]. Etretinate has been shown to be more effective than acitretin at the same dose [104-107]. However, acitretin has a shorter half-life and lower lipophilia than etretinate [108]. For this reason, only acitretin is available as a systemic retinoid in most European countries and has been so since 1988.

Approved indications for acitretin are severe psoriasis that cannot be managed by topical treatments or phototherapy, as well as erythrodermic or pustular psoriasis.

Table 12: Tabular summary

Retinoids	
Approval for psoriasis	1992 (Germany)
Recommended controls	Full blood count, liver enzymes, serum creatinine, pregnancy test (urine), fasting blood sugar, triglycerides/cholesterol/HDL, X-ray examination of bones in case of long-term therapy and complaints
Recommended initial dose	0.3-0.5 mg/kg daily for 4 weeks; then 0.5-0.8

	mg/kg daily
Recommended maintenance dose	Individual dose dependent on response and tolerance
Clinically significant response expected after	4-8 weeks
Response rate	Widely variable and dose-dependent, no definite information possible; partial remission (PASI 75) in 25-75% of patients (30-40 mg daily) in studies (level of evidence 3)
Absolute contraindications	Renal and liver damage; desire to have children in female patients; concomitant medications that interfere with retinoids; concomitant hepatotoxic drugs; pregnancy; breastfeeding; excessive alcohol abuse; blood donation
Important side effects	Vitamin A toxicity (cheilitis, xerosis, nose bleeds, alopecia, increased skin fragility)
Important drug interactions	Phenytoin, tetracyclines, methotrexate, alcohol, mini-pill, lipid-lowering drugs, antifungal imidazoles, vitamin A
Special issues	Contraception up to 2 years after discontinuation in female patients of child-bearing age

Mechanism of action

The exact mechanism of action of retinoids has still not been completely clarified. Retinoids bind receptors belonging to the steroid receptor superfamily. The complex ligand/receptor then binds to specific gene regulatory regions to modulate gene expression. Retinoids have antiproliferative and immunomodulatory properties. In the skin, acitretin reduces the proliferative activity and favours the differentiation of epidermal keratinocytes. Retinoids inhibit keratinocyte production of vascular endothelial growth factor [109], and can exert several anti-inflammatory properties, including the reduction of intraepidermal migration of neutrophils. Retinoids also inhibit IL-6-driven induction of Th17 cells, which play a pivotal role in psoriasis pathogenesis and promote the differentiation of T regulatory cells [110]. After oral intake, between 36% and 95% of acitretin is absorbed in the intestine. Because acitretin binds to albumin, is not very lipophilic, and is not stored in fatty tissue, it is excreted more quickly than etrenitate. However, a small amount of acitretin is converted to etretinate, and this conversion is enhanced by ethanol.

Dosing regimen

A relatively low dose of 0.3-0.5 mg/kg daily is recommended as the initial dose. After three to four weeks, the dose is increased or decreased depending on efficacy and tolerance. The dose generally varies between 0.5-0.8 mg/kg daily with a maximum dose of 1 mg/kg daily. In general, the dose during the first three months of treatment is increased until patients experience a slight scaliness of the lips, which is a useful clinical indicator of sufficient bioavailability [111].

For long-term treatment, a maintenance dose is used that is tolerated by the individual patient and has sufficient efficacy. The duration of maintenance treatment depends on improvement and tolerance in the individual patient.

Generally, in patients with chronic plaque psoriasis, a combination treatment is selected (acitretin + topical treatment, or acitretin + photo(chemo)therapy) in order to achieve sufficient efficacy. In patients with erythrodermic psoriasis or pustular psoriasis, monotherapy with acitretin is advised [112, 113].

Efficacy

A total of seven studies fulfilled the criteria for inclusion in the guidelines [98, 105, 114-118]; of those investigating monotherapy, one was assigned a grade of evidence of A2 [105] and two a grade of evidence of B [114, 116]. Because the efficacy of acitretin in the studies varied greatly, and because hetreogenous study populations and varying definitions of therapeutic success make the assessment of the efficacy of therapy with acitretin difficult, this translates into an overall level of evidence of 3.

Kragballe et al (grade of evidence A2) treated 127 patients with acitretin for 12 weeks. During the first four weeks, doses of 40 mg daily were administered, followed by 0.54 mg/kg daily. PASI scores decreased by an average of 75.85 over 12 weeks of therapy. Complete remission was described in 11% of patients [105]. To a small degree, other forms of psoriasis (e.g. pustular psoriasis) were also included in this study.

Van de Kerkhof et al (grade of evidence B) treated 59 patients with acitretin 20 mg daily, which was increased in 14-day intervals up to 70 mg; after 12 weeks, 41% of the patients experienced a clear improvement or complete clearance of skin lesions. In a study by Gupta et al (grade of evidence B) with 24 patients, treatment with acitretin 10 mg or 25 mg daily did not lead to any improvement in skin lesions, whereas doses of 50 mg and 75 mg daily resulted

in an improvement of at least 75% in 25% of the patients. The increase in adverse drugs reactions with increasing dosages made it difficult to treat with effective drug concentrations and led to high drop-out rates in studies. With low doses up to 20 mg daily, none or only mild adverse drug reactions were observed, but a satisfactory response could not be obtained [112, 119, 120].

Adverse drug reactions/safety

Side effects that have been reported for acitretin treatment in the literature are listed in Table 13. All side effects are reversible except for hyperostosis.

Women of child-bearing age with a desire to conceive are excluded from acitretin treatment. Breastfeeding is also an absolute contraindication. In children treated with acitretin, it is advisable to monitor growth at regular intervals.

Dryness of skin and mucosa can be improved by lubricating the skin and using eye drops. Contact lenses should be avoided. It is important that patients be informed about the possibility of hair loss and the fact that retinoid-induced hair loss is reversible. Photosensitivity during retinoid treatment requires avoidance of excessive sun exposure and the use of sunscreens. In order to prevent elevation of serum lipids and liver enzymes, alcohol abstinence and a low-fat and low-carbohydrate diet are advised. In case of hyperlipidaemia, serum lipids must be monitored frequently and, if necessary, acitretin should be discontinued. The use of lipid-lowering agents (e.g. gemfibrozil or statins) may be associated with an increased risk of myotoxicity. In case of bone pain or decreased mobility, X-ray examination is indicated. In patients with muscle pain, excessive athletic activity must be avoided and NSAIDs are indicated.

Table 13: Overview of important side effects

Very frequent	Vitamin A toxicity (xerosis, cheilitis)
Frequent	Conjunctival inflammation (cave: contact lenses), hair loss, photosensitivity, hyperlipidaemia
Occasional	Muscle, joint, and bone pain, retinoid dermatitis
Rare	Gastrointestinal complaints, hepatitis, jaundice. Bone changes with long-term therapy
Very rare	Idiopathic intracranial hypertension, decreased colour vision and impaired night vision

Important contraindications/restrictions on use

Absolute contraindications

- Severe renal or hepatic dysfunction
- Hepatitis
- Women of child-bearing age: pregnancy, breastfeeding, desire to have children or insufficient guarantee of effective contraceptive measures up to two years after discontinuation of therapy.
- Excessive alcohol abuse
- Comedication that is contraindicated
- Blood donation

Relative contraindications

– Alcohol abuse [121]
– Diabetes mellitus
– Wearing contact lenses
– Childhood
– History of pancreatitis
– Hyperlipidaemia (particularly hypertriglyceridaemia) and drug-controlled hyperlipidaemia
– Arteriosclerosis

Drug interactions

Several drugs may interfere with retinoid metabolism or retinoid effects (Table 14).

Table 14: List of most important drugs with potential interactions

Drug	Type of interaction
Tetracycline	Induction of idiopathic intracranial hypertension
Phenytoin	Plasma protein displacement
Vitamin A	Augmentation of retinoid effect
Methotrexate	Liver toxicity
Low-dose progesterone pills	Insufficient contraceptive effect
Lipid-lowering drugs	Increased risk of myotoxicity
Antifungal imidazoles	Liver toxicity

Instructions for use

Necessary measures
Pre-treatment • Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • History and clinical examination should focus on musculoskeletal problems. If patient reports complaints, further imaging investigation may be performed • Exclude pregnancy/breastfeeding: patient must be informed explicitly and extensively about the teratogenic risk of the medication, the necessity of effective long-term contraception, and the possible consequences of a pregnancy while taking retinoids; written documentation of this informational interview • Inform patients about specific risk of alcohol • Note that during and up to one year after treatment, blood donation is not permitted • Laboratory controls (see Table 15, page 49) During treatment • Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • Take capsules with a fatty meal or with whole milk • Avoidance of pregnancy is mandatory. Start treatment on second or third day of the menstrual cycle, after satisfactory contraception for at least one month prior to treatment. Double contraception is recommended (e.g. condom + pill; IUD/Nuva Ring + pill; cave: no low-dosed progesterone preparations/mini-pills) during and up to two years after end of therapy; effectiveness of oral contraceptives is reduced by acitretin • Avoidance of alcohol • Ask patient about spine and joint complaints at follow up visits. If patient reports complaints, further imaging investigation may be performed • Laboratory controls (see Table 15, page 49) Post-treatment

- Reliable contraception in women of child-bearing age for up to two years after therapy
- Double contraception, as described above, is recommended
- Patients may not donate blood for up to one year after the discontinuation of therapy

Overdose/measures in case of overdose

Because acitretin has low acute toxicity, adverse drug reactions following overdose are usually reversible after discontinuation of the preparation. Headache, nausea and/or vomiting, fatigue, irritability, and pruritus are symptoms of acute overdose.

Measures in case of overdose:

- Discontinue retinoids
- Monitor vital parameters, liver and renal function, electrolytes
- Consult other specialists to manage side effects beyond dermatological expertise

Table 15: Lab controls

	Period in weeks						
Parameter	Pre-treatment	1	2	4	8	12	16
Blood count*	x				x		x
Liver enzymes**	x			x	x		
Serum creatinine	x						
Pregnancy test (urine)	x	Monthly up to 2 years after therapy					
Fasting blood sugar	x						
Triglycerides, cholesterol, HDL	x			x			x
Further specific testing may be required according to clinical signs, risk, and exposure.							

*Hb, Hct, leucocytes, platelets

**AST, ALT, AP, γGT

Special considerations

Contraception

Because the effectiveness of oral contraceptives is reduced by acitretin, microdosed progestin preparations and low-dose progesterone preparations must be avoided. Double contraception is recommended (e.g. condom + pill; IUD/Nuva-Ring + pill; cave: NO low-dosed progesterone preparations/minipills). Monthly pregnancy tests are recommended in women of childbearing age. Contraception is mandatory in women during and up to two years after discontinuation of therapy.

Increase in liver enzymes under acitretin treatment

Increases in liver enzymes during acitretin treatment are a challenge. Indeed, a clear upper limit for liver enzyme levels would facilitate monitoring. However, increases in liver enzymes are often transient. Therefore, in cases of increased liver enzyme levels, the blood test must be repeated. It is important to discontinue treatment if there is a trend towards increasing levels. An arbitrary, maximum acceptable level can be defined locally.

Combination therapy

In the treatment of chronic plaque psoriasis, acitretin is frequently prescribed in combination with calcipotriol or photo(chemo)therapy. Combination treatment with calcipotriol shows increased efficacy with lower doses of acitretin (grade of evidence B) [98]. Although anecdotal reports suggest that the combination of acitretin and biologicals is effective [122], further studies are required.

Table 16: Possibilities for therapeutic combination

	Recommendation	Comments
Phototherapy	++	Increased efficacy with reduced cumulative doses of UV (grade of evidence A-C) [115, 117, 118]
Methotrexate	-	Increased hepatotoxicity
Ciclosporin	-	No evidence of increased efficacy
Fumaric acid esters	-	No evidence of increased efficacy
Efalizumab	+/-	Case reports of successful combination exist [123]
Etanercept	+	One RCT showing similar efficacy for acitretin in combination with 1 x 25 mg etanercept versus 2 x

		25 mg etanercept [122]
Other biologics	+/-	Evidence restricted to anecdotal reports [123]

Summary

According to the seven evaluated studies, no definite conclusion can be drawn with regard to the efficacy of retinoids in the treatment of psoriasis vulgaris (level of evidence 3). Although evidence for the efficacy of combination treatment with retinoids and other anti-psoriatic therapies is limited, the value of the combination of calcipotriol and photo(chemo)therapy is supported by successful clinical practice.

Except for bone toxicity and teratogenicity, the side effects can be regarded as mild and are reversible. However, the tolerability of mucocutaneous side effects is limited at higher doses.

Therapeutic recommendations

- Acitretin is not suggested as a first choice for monotherapy among the conventional systemic treatments.
- The treatment of women of child-bearing age is strongly discouraged due to the teratogenic potential of acitretin.

3.4 Fumaric acid esters

Mrowietz/Eberlein

Introduction/general information

Systemic therapy with fumaric acid esters/fumarates has been licensed in Germany since 1994. The preparations Fumaderm® initial and Fumaderm® are available as standardized drugs. Both preparations contain a mixture of dimethyl fumarate (DMF) and three salts of ethyl hydrogen fumarate. DMF is considered to be the active ingredient. Fumaderm® is the only licensed product. Fumaderm® initial and Fumaderm® differ only in the amount of DMF they contain (Fumaderm® initial: 30 mg DMF per tablet; Fumaderm®: 120 mg DMF per tablet).

That fumarates have a clinical effect on psoriasis vulgaris has been known since 1959, when individual prescriptions were commonly used. Although the use of fumarates on psoriasis has also been evaluated in clinical trials, only a small number of these have followed the criteria of evidence-based medicine.

Treatment of severe psoriasis with fumarates (Fumaderm®) follows an established dosing regimen, which is part of the treatment recommendation.

Table 17: Tabular summary

Fumaric acid esters	
Approval for psoriasis	1994 (Germany)
Recommended controls	Serum creatinine, transaminases/GGT, complete blood count, urine status, pregnancy test
Recommended initial dose	See Table 18, page 53
Recommended maintenance dose	Individually adapted dosage
Clinically significant response expected after	6 weeks
Response rate	PASI 75 in 50-70% of patients by the end of the induction phase (i.e. after 16 weeks)
Absolute contraindications	Severe diseases of the gastrointestinal tract and/or the kidneys; pregnancy or breastfeeding (lack of experience)
Important side effects	Gastrointestinal complaints, flush, lymphopenia, eosinophilia
Important drug interactions	None known
Special considerations	Particularly suitable for long-term treatment

Mechanism of action

The active component of Fumaderm®, dimethyl fumarate (DMF), is rapidly metabolized, and monomethyl fumarate can be detected in the blood as a major metabolite. The interaction of DMF with intra- and extracellular thiols, namely glutathione, is considered the primary mechanism of action. Shifting the balance of oxidized to reduced glutathione is known to inhibit redox-sensitive kinases, which subsequently inhibits phosphorylation and ubiquitination of the inhibitor of nuclear factor kappa B (I-κB), leading to a diminished translocation of nuclear factor kappa B (NF-κB) from the cytosol into the nucleus. Through this, the NF-κB-mediated transcription of intracellular mediators (e.g. tumor necrosis factor

alpha (TNF-α) or interleukin 8 (IL-8)) and of adhesion molecules (e.g. E-selectin, ICAM-1, and VCAM-1) is inhibited. It has been previously reported that the expression of such cytokines and adhesion molecules can be inhibited by DMF in vitro.

DMF and the monoester inhibit the maturation of dendritic cells, which play an important role in the development and maintenance of immunologic reactions that lead to an inflammatory response. Other work describes the shift of the secretion of Th1-cytokines to a Th2-type pattern by monomethyl fumarate.

An important property of DMF is its ability to induce apoptosis, particularly in activated T cells, but also, at higher concentrations in vitro, in all types of cells investigated.

Dosing regimen

A slow increase in dose according to the established dosing regimen is considered the standard for treatment (Table 18). This approach is meant to improve tolerance, especially with regard to the gastrointestinal tract.

Individual dose adjustment is necessary and depends on therapeutic response and possible adverse drug reactions. The highest recommended dose is 1.2 g daily Fumaderm® (equals 720 mg DMF, six tablets Fumaderm®); however, not all patients require this dose for effective treatment. Most patients are treated with between two and four tablets of Fumaderm® daily under maintenance conditions. When starting treatment with Fumaderm®, the dose is increased until a satisfactory clinical response is achieved. The individual maintenance dose is then found by reducing the dose gradually.

Treatment with fumarates can be stopped abruptly; rebound phenomena or pustular exacerbations do not occur following discontinuation.

Table 18: Dosage scheme for Fumaderm® initial/Fumaderm®

	30 mg dimethyl fumarate (Fumaderm® initial) - Number of tablets per day	120 mg dimethyl fumarate (Fumaderm®) - Number of tablets per day
Week 1	0-0-1	-
Week 2	1-0-1	-

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

Efficacy

A total of nine studies fulfilled the criteria for inclusion in the guidelines [124-132]. Two of the studies were assigned a grade of evidence of A2 [125, 128], two a grade of evidence of B [129, 132], and five a grade of evidence of C [124, 126, 127, 130, 131]. Because the outcome measures in these studies were heterogeneous, this results in a level of evidence of 2.

In the included studies, reductions between 50% and 80% were observed in patients on Fumaderm® therapy after up to 16 weeks of treatment. In the study by Altmeyer et al (grade of evidence A2), in which Fumaderm® was investigated in a larger cohort of patients ($N = 50$), a reduction in PASI of 50.2% was seen in patients with severe psoriasis vulgaris after 16 weeks [125]. In a study comparing Fumaderm® monotherapy with a combination of Fumaderm® and topical calcipotriol ointment, Gollnick et al (grade of evidence A2) observed a reduction in PASI of 51.9% after 13 weeks [128].

In a long-term treatment study by Altmeyer et al (grade of evidence C), a reduction in PASI of 79.1% was demonstrated after a 16-week induction phase [124]. In a very small collective of 13 patients with psoriasis vulgaris, Bayard et al (grade of evidence C) showed substantial improvement or clearance in 45% of cases after 12 weeks of treatment [126]. In a study by Nugteren-Huying et al (grade of evidence B), 75% of the patients achieved a reduction in affected skin area of more than 70% [132]. In a study comparing Fumaderm® and DMF monotherapy, Kolbach et al (grade of evidence B) showed that 53% of patients of the Fumaderm® group experienced an improvement in skin symptoms of more than 75% [129]. These data were confirmed by Litjens et al (grade of evidence C) in 20 patients treated with Fumaderm® over a period of 20 months [130]; after 12 weeks of therapy, there was a reduction in PASI of 53.3%. In a study by Carboni et al (grade of evidence C) with 40 patients, therapy with Fumaderm® resulted in a substantial improvement of skin symptoms or in clearance in

71% of patients after 12 weeks [127]. In an open-label study by Mrowietz et al (grade of evidence C), an 80% reduction in PASI among patients with severe psoriasis was observed after 16 weeks [131].

When Fumaderm® is used to treat psoriasis vulgaris according to the established dosing schedule, clinically meaningful improvement is seen after 6 to 8 weeks of therapy; this improvement continues during prolonged treatment.

Adverse drug reactions/safety

Gastrointestinal complaints (which occur in up to 60% of patients, particularly in the first weeks after initiation of therapy) and flush symptoms are the most frequent adverse drug reactions during treatment with fumarates. Gastrointestinal tolerance may be improved by taking the tablets with milk. The administration of acetylsalicylic acid can help to decrease flush symptoms. Gastrointestinal symptoms consist mainly of diarrhoea, increased stool frequency, nausea, and abdominal cramps. Flush may occur with a broad spectrum of symptoms, such as a feeling of warmth, reddening of the face, and headache lasting for minutes to hours.

Leucocytopenia, lymphocytopenia, and eosinophilia can be observed during therapy with fumarates. If leucocytes drop below 3000/µl and lymphocytes below 500/µl, the dose must be reduced or the treatment stopped. An increase in eosinophils is temporary and is usually observed between weeks 4 and 10 of treatment. Occasionally, proteinuria occurs during Fumaderm® therapy, but disappears after dose reduction or cessation of treatment. In rare cases, an isolated increase in ALT or bilirubin may be seen.

To date, opportunistic infections or an increased tendency towards infection have not been observed. Fumarates have not been shown to impair antibacterial defence mechanisms in cells of the innate immune system in vitro.

Results from open-label studies are available for patients with psoriasis vulgaris who have been treated with Fumaderm® over a period of one year. Along with very good efficacy, no adverse drug reactions leading to treatment discontinuation have been observed in association with long-term treatment. Some psoriasis patients have been treated continuously for up to 14 years with Fumaderm®; neither the development of malignancies nor an increased susceptibility to infections was observed [133].

Dose adjustments are not required in elderly patients or in patients with impaired liver function.

Although no reports are available on the use of fumarates during pregnancy or breastfeeding, there is no toxicological evidence of teratogenic or mutagenic effects for fumaric acid esters.

Table 19: Overview of important side effects

Very frequent	Diarrhoea, flush
Frequent	Abdominal cramps, flatulence, lymphocytopenia, eosinophilia
Occasional	Nausea, dizziness, headache, fatigue, proteinuria, increase in serum creatinine, increase in liver enzymes
Rare	Isolated increases in ALT or bilirubin

Important contraindications/restrictions on use

Absolute contraindications

- Severe disease of the gastrointestinal tract and/or the kidneys
- Pregnancy or breastfeeding (lack of experience)

Relative contraindications

– Haematological disease

Drug interactions

There are no known drug interactions with fumaric acid esters.

Because fumarates may impair renal function, drugs with known nephrotoxic potential should not be used concomitantly.

Instructions for use

Necessary measures
<u>Pre-treatment</u> • Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • History and clinical examination

- Laboratory controls (see Table 20, page 57)

During treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Clinical examination
- Laboratory controls (see Table 20, page 57)

Post-treatment

None

Table 20: Lab controls

	Period in weeks/months		
Parameter	Pre-treatment	Months 1-6 every 4 weeks	As of month 6, Thereafter, every 4 weeks
Blood count	x	x	x
Liver enzymes	x	x	x
Serum creatinine	x	x	x
Urine sediment	x	x	x
Pregnancy test	x		
Further specific testing may be required according to clinical signs, risks, and exposure.			

Special considerations

Because fumarates are not registered in all European countries, off-label use is common.

Combination therapy

The combination of fumarates with other systemic medication is currently not recommended, mainly due to a lack of experience. In case reports, the successful combination of Fumaderm® with methotrexate or ciclosporin has been described [70].

Fumaderm® may be combined with any topical anti-psoriatic medication. The combination of Fumaderm® and calcipotriol was found to be synergistically beneficial in a randomized clinical trial [128].

UV light (UVB, PUVA) can be combined with Fumaderm® initial during the first three weeks of treatment.

Table 21: Possibilities for therapeutic combination

	Recommendation	Comments
Methotrexate	-	Case reports of successful combination treatment exist [70]
Ciclosporin	-	Case reports of successful combination treatment exist [70]
Retinoids	-	No evidence of increased efficacy
Biologics	-	Lack of experience
Phototherapy	+	Only during treatment with Fumaderm® initial (i.e. the first three weeks of treatment)

Summary

Of the 13 studies evaluated, nine fulfilled the criteria for inclusion in the guidelines. After 16 weeks, 50% to 70% of patients achieved a PASI 75 response (level of evidence 2). Good efficacy was observed both in induction and long-term therapy. The treatment of psoriasis vulgaris with fumaric acid esters represents an effective systemic treatment that demonstrates a high level of long-term safety. Tolerance is limited by gastrointestinal adverse effects and flush symptoms. The risk-benefit analysis of fumarates is positive, and practicability for both physicians and patients is good. Positive aspects of treatment with fumarates are the lack of drug-drug interactions, the absence of immunosuppressive effects, and the fact that long-term treatment does not lead to an increased risk of infections or malignancies. Combination treatment with topical therapies is recommended.

Therapeutic recommendations

- Treatment with fumaric acid esters is suggested as an effective induction therapy for moderate to severe psoriasis vulgaris in adult patients.
- Treatment is limited by gastrointestinal adverse effects and flush symptoms.

- A combination of fumaric acid esters and topical treatments is recommended.
- Because of the favourable risk-benefit profile with good safety during long-term treatment, fumarates are suggested.*

** For this point, a consensus (defined as agreement by at least 75% of the voting experts) could not be reached. The percentage of positive votes in this case was 64%.*

3.5 Adalimumab

Ortonne/Thio

Introduction/general information

Adalimumab (Humira®) is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody containing only human peptide sequences [134-136]. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab consists of human heavy- and light-chain variable regions, that confer specificity to human TNF, as well as of human IgG1 heavy-chain and kappa light-chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not to lymphotoxin (TNF-β) [134-136].

Table 22: Tabular summary

Adalimumab	
Approval for psoriasis	December 2007 (EMEA)
Recommended controls	Blood count, liver enzymes, ESR/CRP, serum creatinine, urine sediment, pregnancy test (urine), HBV/HCV, HIV (prior to therapy), tuberculosis screening including chest X-ray (prior to therapy)
Recommended initial dose	Loading dose at baseline: 80 mg subcutaneous
Recommended maintenance dose	40 mg subcutaneous every other week
Clinically significant response expected after	4 weeks
Response rate	PASI 75 in 53-80%
Absolute contraindications	Concomitant immunosuppressive therapy; active chronic hepatitis B; active tuberculosis; localized infections; congestive heart failure (NYHA III / IV)

Important side effects	Injection-site reactions; infections; drug-induced lupus; lymphoma (very rare)
Important drug interactions	Abatacept, anakinra
Special considerations	See subchapter

Mechanism of action

Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF [134-136]. After treatment with adalimumab, levels of acute-phase reactants of inflammation (C-reactive protein [CRP], erythrocyte sedimentation [ESR]) and serum cytokines rapidly decrease [134-138].

Pharmacokinetics/pharmacodynamics

After a single 40 mg subcutaneous dose to healthy adults, the maximum serum concentration (4.7 ± 1.6 microgram/mL) is achieved within 131 ± 56 hours [134-136]. The average absolute bioavailability is 64%. A proportional increase in serum adalimumab steady-state trough concentrations occurs with once-weekly subcutaneous administration. Adalimumab displays linear kinetics over the dose range of 0.5-10 mg/kg after a single intravenous dose to patients with rheumatoid arthritis. Distribution of adalimumab is largely confined to the vascular department. The mean terminal half-life was 11.8 days after a dose of 0.5 mg/kg and 13.3 days after a dose of 10 mg/kg. Only a small fraction of adalimumab clearance variance could be explained by patient body weight, which suggests the appropriateness of a fixed total body dose for all patients; however, there are no data on patients who weigh more than 100 kg [134-138].

Dosing regimen

Adalimumab is administered subcutaneously. According to the two clinical trials that fulfilled the criteria for inclusion in the guidelines (see Efficacy section below), the recommended dosing regimen includes one 80 mg subcutaneous injection at the initiation of treatment, followed by 40 mg subcutaneously every other week for maintenance treatment, beginning one week after the induction dose [134-136].

Efficacy

Two studies by different authors investigating the efficacy of adalimumab fulfilled the criteria for inclusion in the guidelines and were assigned a grade of evidence of A2 [139, 140]. This translates into an overall level of evidence of 1.

One study was a 12-week, randomized, double-blind, placebo-controlled trial [139]. The study population consisted of 147 adult subjects with stable, moderate to severe chronic plaque psoriasis defined as BSA ≥ 5%. Subjects were randomized to receive (1) an 80 mg subcutaneous loading dose of adalimumab at week 0 followed by 40 mg subcutaneously every other week beginning at week 1; (2) an 80 mg loading dose at weeks 0 and 1 followed by 40 mg per week subcutaneously beginning at week 2; or (3) matching placebo injections. After 12 weeks of study treatment, a total of 53.3% of subjects who received adalimumab 40 mg every other week, and 80.0% of subjects who received adalimumab 40 mg weekly, achieved a PASI 75 response compared with 3.8% of subjects who received placebo (*P* <0.001 vs. placebo, modified ITT population). Adalimumab also demonstrated a clinically relevant and statistically significant improvement in quality of life among patients with moderate to severe psoriasis, as shown by a variety of secondary efficacy endpoints.

In this same study, a 48-week extension phase for patients completing the initial 12 weeks was performed to investigate the long-term efficacy and safety of adalimumab; 72% of patients who had participated in the initial phase went on to complete 60 weeks of treatment. All 137 subjects who entered this study either continued to receive their previous dose of adalimumab (40 mg every other week or 40 mg weekly, both by subcutaneous injection) through week 12 or were switched to an 80 mg subcutaneous dose of adalimumab at week 12 and a 40 mg subcutaneous dose of adalimumab every other week beginning at week 13 (patients previously receiving placebo). Weeks 25-60 were an open-label phase during which the patients in the placebo/every-other-week group and the every-other-week group were eligible for dosage escalation (to adalimumab 40 mg weekly) if they had achieved less than a PASI 50 response. Both adalimumab 40 mg every other week and adalimumab 40 mg weekly were highly effective. A PASI 75 at week 60 was seen in 64%, 56%, and 45% of patients receiving adalimumab 40 mg weekly, adalimumab 40 mg every other week, and previously placebo treated patients, respectively. Regarding patient-reported outcomes, adalimumab continued to be effective in improving quality of life in subjects with moderate to severe chronic plaque psoriasis for up to 60 weeks of treatment.

The second study was a 52-week, randomized, double-blind, placebo-controlled, multicentre trial evaluating both the short-term (16 weeks) and long-term (52 weeks) clinical efficacy and safety of a 40 mg dose of adalimumab administered subcutaneously every other week in subjects with moderate to severe chronic plaque psoriasis [140]. Furthermore, the time to loss of adequate response was evaluated (defined as <PASI 50 response after week 33 and an at least six-point increase in the PASI score relative to the PASI score at week 33). The study was composed of three distinct study periods: During Period A (weeks 1-15), patients received an 80 mg loading dose of adalimumab at week 0 followed by 40 mg every other week starting at week 1 (814 patients) or matching placebo injections (398 patients) for the evaluation of efficacy and safety. During Period B (weeks 16-32), patients received open-label adalimumab at a dose of 40 mg every other week for the evaluation of long-term response. To be eligible to continue in the open-label portion of the study (i.e. Period B), patients had to show a PASI 75 response at week 16 (580 adalimumab treated patients and 26 placebo treated patients from period A). During Period C (weeks 33-52), patients were re-randomized to 40 mg every other week or to matching placebo as a way to evaluate time to loss of adequate response. Week 33 PASI 75 responders (490 patients) continued to receive adalimumab 40 mg every other week or matching placebo in a blinded fashion. The first primary end point was the PASI 75 response rate at week 16 (71% in the adalimumab group; 7% in the placebo group). The second primary end point was the proportion of subjects who lost an adequate response after week 33 and on or before week 52 (28% in the group re-randomized to placebo; 5% in the group re-randomized to adalimumab). During Period B, across all endpoints including PASI, PGA, and DLQI, the majority of subjects who were originally randomized to adalimumab maintained their response to treatment, while subjects who were originally randomized to placebo showed an improvement in their responses following adalimumab treatment. The primary efficacy endpoints were conducted on the ITT population.

Adverse drug reactions/safety

In placebo-controlled trials, injection-site reactions (erythema, itching, pain, swelling, haemorrhage) were the most frequently reported adverse drug reactions, occurring in 20% of patients treated with adalimumab compared to 14% of patients receiving placebo. The use of adalimumab can be associated with infectious adverse effects. These consisted primarily of upper respiratory tract infections, bronchitis, and urinary tract infections. More serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis. Adverse reactions of the haematologic system, including thrombocytopenia and leucopenia, have been infrequently

reported with adalimumab. Other rare side effects of adalimumab are severe allergic reactions (rash; hives; itching; difficulty in breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue). Treatment with adalimumab may result in the formation of autoantibodies and rarely in the development of lupus-like syndrome. Malignancies, especially lymphoma, associated with the use of adalimumab occur very rarely (see Special considerations) [134-138]. However, with adalimumab being the newest available biologic at present there is insufficient long-term data on the safety of this drug in patients with plaque-type psoriasis.

Side effects may be especially likely to occur in elderly patients, who are usually more sensitive than younger adults to the effects of adalimumab. Adalimumab causes more serious infections and malignancies in the elderly. No pharmacokinetic data are available in patients with hepatic or renal impairment. Adalimumab has not been studied in paediatric patients.

Although preliminary data suggest that there is no increased risk for adverse pregnancy outcomes in women exposed to adalimumab during the first trimester, initiation of adalimumab is not recommended during pregnancy (pregnancy category B for all trimesters). There are no adequate studies in women for determining infant risk when using this medication during breastfeeding.

Table 23: Overview of important side effects

Very frequent	Injection-site reaction
Frequent	Upper respiratory tract infections, sinusitis, injection-site reactions, headache, and rash
Occasional	Tuberculosis
Rare	
Very rare	Drug-induced lupus, lymphoma

Important contraindications/restrictions on use

Absolute contraindications

- Concomitant immunosuppressive therapy
- Active chronic hepatitis B
- Localized infections
- Active tuberculosis

- Congestive heart failure (NYHA grade III/IV)
- Pregnancy/breastfeeding

Relative contraindications

– History of recurrent infections
– Underlying conditions predisposing to infections
– Patients living in geographical areas where tuberculosis and histoplasmosis are widespread
– Psoriasis patients with concomitant systemic lupus erythematosus or multiple sclerosis
– Live vaccines
– Hepatitis C
– PUVA >200 treatments (especially if followed by ciclosporin use)
– Malignancies and lymphoproliferative disorders

Drug interactions

Serious infections are more likely to occur when adalimumab is combined with anakinra or abatacept. Live-attenuated vaccines should not be administered during treatment with any of the biologic agents. Depending on their half-life, biologics should be discontinued four to eight weeks prior to an immunization and may be restarted two to three weeks later.

Table 24: List of most important drugs with potential interactions

Drug	Type of interaction
Anakinra	Increased risk of serious infections
Immunosuppressive drugs (ciclosporin, MTX, other biologicals)	Increased immunosuppression
PUVA	Skin cancer risk

Instructions for use

Necessary measures
Due to the lack of long-term data, the guidelines development group feels that caution is advisable and monitoring during treatment should be performed. <u>Pre-treatment</u> • Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)

- HRQoL (such as DLQI/Skindex-29 or -17)
- History and clinical examination should focus on prior exposure to treatments, malignancies, infections, congestive heart failure and neurological symptoms
- Recommended measures include:
  - Check for skin cancer
  - Check for lymphadenopathy
  - Laboratory parameters (see Table 25, page 66)
  - Urine analysis
  - Chest X-ray
  - Mantoux test and/or QuantiFERON®-TB Gold test® test
  - In case of doubt, contact specialist
  - Pregnancy test
- Contraception

<u>During treatment</u>

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Clinical examination should focus on malignancies, risk factors for serious infections, congestive heart failure, and neurological symptoms
- Recommended measures include:
  - Check for skin cancer
  - Check for lymphadenopathy
  - Laboratory parameters (see Table 25, page 66)
  - Urine analysis
- Contraception

<u>Post-treatment</u>

- After discontinuation of adalimumab, patients should be followed up with medical history and physical examination
- Reliable contraception until five months after treatment, if applicable (according to the label)
- Physicians are encouraged to enrol their patients in a registry (if available)

Overdose/measures in case of overdose

Dose-limited toxicity has not been studied in clinical trials. The highest examined dose was multiple intravenous infusions at 10 mg/kg [141].

Table 25: Lab controls

	Period in weeks			
Parameter	Pre-treatment	4	12	Thereafter, every 3 months
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x	x	x	x
Urine sediment	x	x	x	x
Pregnancy test (urine)	x	x	x	x
ESR, CRP	x	x	x	x
HBV/HCV	x			
HIV	x			
Further specific testing may be required according to clinical signs, risks, and exposure.				

Special considerations

Adalimumab can be given to patients with moderate to severe chronic plaque-type psoriasis who were previously non-responsive to other anti-TNF-α agents. Treatment with adalimumab should be discontinued after 12 weeks in psoriasis patients whose skin lesions have not shown an adequate response (i.e. at least a PASI 50 response) when assessed using the PASI score.

TBC and TBC screening

Potential recipients of TNF antagonists should be rigorously screened with skin testing, detailed questioning about potential tuberculosis exposure (including recent travel), assessment for symptoms such as cough and weight loss, and chest radiography (see Instructions for use table, page 64). A Mantoux test and/or QuantiFERON®-TB Gold test® test should be performed at baseline. Use of the QuantiFERON®-TB Gold test® is suggested in patients whose Mantoux test result is uncertain. The tuberculin skin test (TST) is the current gold standard, but has several limitations, including the need for two visits to the

clinic (intradermal injection and 48 to 72 hours later); a sensitivity and specificity of 74% and 81%, respectively; its being subject to interrater variability; difficulty in interpreting results in patients who have received BCG vaccination in the past; potential unreliability in patients on an immunosuppressive therapy; false positive results in approximately a quarter of cases [142]. The QuantiFERON®-TB Gold test® may be the future gold standard in TBC testing [142]. Approved by the FDA for the diagnosis of latent and chronic tuberculosis in 2005, the test detects IFN-gamma release by TBC antigen-sensitized white blood cells. Its sensitivity is 89% and specificity 98.1%. Each test costs approximately US $200.

Corresponding monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy. Particular care should be taken when patients come from areas where certain opportunistic infections are endemic. As with other immunosuppressive drugs, TNF antagonists should not be given to patients with active infections. If latent tuberculosis is suspected, adalimumab therapy may be initiated in combination with prophylactic treatment, preferably isoniazid, started one month before adalimumab therapy and continued for nine months. The presence of active tuberculosis is an absolute contraindication for therapy with TNF antagonists.

Hepatitis/HIV

Although not mandatory, testing for HIV and hepatitis B and C infection is desirable, especially in patients who are at higher risk. Because of the risk of reactivation, chronic carriers of hepatitis B should not be treated with adalimumab. Patients with hepatitis C should be appropriately evaluated and monitored during therapy with adalimumab.

Malignancies

Although it is presently unknown whether psoriasis patients treated with TNF antagonists have a higher risk of lymphoma or skin cancer, a potential risk for the development of lymphoma or other malignant diseases cannot be excluded based on current knowledge. It should be noted, however, that patients with psoriasis, similar to patients with rheumatoid arthritis, have a higher baseline lymphoma risk compared to the general population [143] and may also carry an increased risk of developing skin cancer due to previous UV phototherapy, particularly PUVA, or to the use of immunosuppressive drugs, such as ciclosporin [95, 96]. As a result, all patients, particularly those with intensive immunosuppressive therapy in their medical history, as well as psoriasis patients with prior PUVA therapy, should be evaluated for non-melanoma skin cancer both before and during TNF-antagonist therapy.

Combination therapy

No clinical studies have been performed investigating the combined use of adalimumab with other therapeutic options in psoriasis. Topical antipsoriatic therapies (corticosteroids and vitamin D) are allowed during adalimumab therapy. There are two anecdotal articles reporting the combination of retinoids and adalimumab [123, 144]. Due to the unknown role of adalimumab in the development of skin malignancies, the combination of adalimumab and phototherapy should be restricted.

Table 26: Possibilities for therapeutic combination

	Recommendation	Comments
Methotrexate	+/-	Under investigation in psoriasis, but common in rheumatology. Decreased adalimumab absorption possible
Ciclosporin	+/-	Increased immunosuppression
Retinoids	+/-	Evidence is restricted to anecdotal reports [123, 144]
Fumaric acid esters	-	Lack of experience
Biologics	-	Increased immunosuppression
Phototherapy	-	In PUVA treated patients, possible increase in skin cancer risk

Summary

Two studies by different authors investigating the efficacy of adalimumab fulfilled the criteria for inclusion in the guidelines and were assigned a grade of evidence of A2. This translates into an overall level of evidence of 1.

Adalimumab is very effective in the treatment of moderate to severe chronic plaque-type psoriasis in adults. Between 53% and 80% of the psoriasis patients treated with adalimumab showed a PASI 75 response at week 16, and almost 14% of patients achieved the maximal PASI 100 response (i.e. complete clearance). The most frequent adverse events were injection-site reactions, upper respiratory tract infection, headache, rash, and sinusitis. Although very rare, serious infections may occur during adalimumab treatment. The potential role of adalimumab in the development of malignancies is unknown.

Therapeutic recommendations

- Adalimumab is recommended for induction therapy for moderate to severe psoriasis if photo(chemo)therapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated.
- If, after 10 to 16 weeks, induction therapy is considered successful, maintenance therapy can be considered with the lowest effective dose.

3.6 Etanercept

Nijsten/Leonardi/Chimenti/Giunta

Introduction/general information

Etanercept is a soluble TNF receptor that binds and neutralizes TNF, a cytokine that plays an important role in several inflammatory diseases such as arthritis, Crohn's disease, and psoriasis. In the European Union, this agent is approved for the treatment of patients with moderate to severe psoriasis who have not responded to other conventional systemic therapies, such as PUVA, MTX, and ciclosporin, or who have contraindications to, or do not tolerate, these therapies.

Table 27: Tabular summary

Etanercept	
Approval for psoriasis	September 2004 (EMEA)
Recommended controls	Full blood count, liver enzymes, serum creatinine, urine analysis, pregnancy test (urine), HBV/HCV, HIV (prior to therapy), tuberculosis screening including chest X-ray (prior to therapy)
Recommended initial dose	2 x 25 or 2 x 50 mg weekly (weeks 0-12)
Recommended maintenance dose	2 x 25 or 1 x 50 mg weekly
Clinically significant response expected after	6-8 weeks
Response rate	PASI 75 in 33% or 49% after 12 weeks (2 x 25 or 2 x 50 mg weekly, respectively)
Absolute contraindications	Pregnancy/breastfeeding, active infections, active tuberculosis, active chronic hepatitis B, demyelinating disease, congestive heart failure (NYHA grade III or IV)

Important side effects	Injection site reactions; antibody formation; bone marrow suppression (thrombocytopenia, (aplastic) anaemia, leucopenia, neutropenia, and pancytopenia); drug-induced lupus erythematodes; demyelinating disease; serious infections including tuberculosis; haematological and solid malignancies.
Important drug interactions	Anakinra
Special considerations	Weight gain

Mechanism of action

Pharmacokinetics

Etanercept is a fully human dimeric fusion protein consisting of the extracellular ligand-binding domain of the TNF-α receptor linked to the Fc portion of human immunoglobulin G1. Etanercept is slowly absorbed from the injection site. The absolute bioavailability is estimated to be about 60%, the mean time to its peak concentration is 51 hours, and its elimination half-life is 68 hours. It distributes widely into tissues. The concentration-time profiles suggest that steady state is reached well before 12 weeks; serum concentrations after 50 mg biweekly are approximately twice as high as those achieved with the 25 mg biweekly dose, and there is minimal to modest accumulation of etanercept after multiple dosing [145]. Etanercept is probably metabolized by proteolytic processes before being recycled or eliminated in bile or urine.

Pharmacodynamics

Etanercept inhibits the activity of TNF-α by competitively binding to this proinflammatory cytokine and preventing interactions with its cell surface receptors. The dimeric nature of etanercept permits binding of the protein to two free, or receptor-bound, molecules of TNF-α, with a very high affinity preventing interactions of these molecules with its cell surface receptors.

Dosing regimen

Initial dose (weeks 0-12):

2 x 25 or 2 x 50 mg weekly

Maintenance dose (weeks 13-24):

if PASI 75 (or minimum PASI 50) is achieved after 12 weeks: 2 x 25 mg weekly

if PASI 75 (or minimum PASI 50) is not achieved after 12 weeks: 1 x 50 mg weekly up to 24 weeks; enbrel may also be used beyond 24 weeks in some patients

Because the long-term safety of etanercept in psoriasis is not well documented and high doses may be associated with higher levels of immunosuppression (i.e. risk of serious infections/malignancies), an attempt should be made to keep cumulative doses low. A recent study showed that the proportion of patients who responded well to etanercept after 12 weeks and subsequently used etanercept continuously up to week 24 was significantly higher than the proportion of 12-week responders who received therapy only at week 16 or 20 if needed due to relapse [146]. However, cumulative doses were lower in the interrupted treatment arm. A cost-effectiveness analysis suggested that use of etanercept was most cost effective among patients with poor baseline HRQoL and those at high risk of hospitalization [147]. Also, this study showed that low-dose, intermittent use of etanercept is substantially less expensive than low-dose continuous or high-dose intermittent administration.

Efficacy

A total of eight studies on monotherapy with etanercept fulfilled the criteria for inclusion in the guidelines; four of these were assigned a grade of evidence of A2 [148-151], three a grade of evidence of B [146, 152, 153] (of which one study [153] was the open-label extension study of [151]), and one a grade of evidence of C [154]. This translates into an overall level of evidence of 1.

In a phase II study involving 57 patients receiving etanercept 25 mg twice weekly compared to 55 patients receiving placebo, Gottlieb et al (grade of evidence A2) demonstrated a reduction in PASI of at least 75% for 30% of patients in the etanercept group compared to 2% of patients in the placebo group after 12 weeks. After 24 weeks, the percentage of patients showing this reduction in PASI score increased to 56% in the etanercept group compared to 5% in the placebo group [148].

In a study with 672 patients, Leonardi et al (grade of evidence A2) demonstrated a PASI 75 response in 14% (25 mg once weekly), 34% (25 mg biweekly), and 49% (50 mg biweekly) of patients treated with etanercept after 12 weeks, compared to an improvement of only 4% in the placebo group. After 24 weeks, the proportion of patients with a PASI 75 response increased to 25%, 44%, and 59%, respectively [149].

Similar treatment effects were shown in the studies by Papp et al, Tyring et al, and Cassano et al [150-152]. After 12 weeks of treatment with etanercept 25 mg biweekly by subcutaneous injection, Papp et al demonstrated a PASI 75 response for 34% and a PASI 90 response for 11% of patients. Continuous treatment with the same dosage increased the number of patients with a PASI 75 response to 45% after 24 weeks. In two studies with a grade of evidence of

A2, treatment with a 50 mg dose of etanercept administered biweekly by subcutaneous injection yielded a PASI 75 response for between 47% and 49% of patients after 12 weeks. A PASI 90 response was shown for 21% of patients in both studies [150, 151]. In the study by Tyring et al, an open-label extension phase was conducted (grade of evidence B), using a dosage of etanercept 50 mg biweekly. The interim 24-week results demonstrated a PASI 75 response for 60% of the patients treated throughout week 24 and for 48% of the patients who switched from placebo to etanercept at week 13 [153].

In the study by Cassano et al (grade of evidence B), 54% of the patients treated with etanercept 50 mg biweekly had a PASI 75 after 12 weeks. A dose of 100 mg once weekly demonstrated no further benefit, with 50% of the patients on this dose having a PASI 75 after 12 weeks [152].

The open-label study by Moore et al (grade of evidence B) evaluated the efficacy and safety of continuous versus interrupted etanercept therapy. During the first 12 weeks, patients in the continuous-therapy and interrupted-therapy groups received the same treatment (i.e. etanercept 50 mg twice weekly by subcutaneous injection) and showed a PGA of ≤ 2 in 71% and 72% of cases at week 12. Starting at week 13, patients in the first study arm continued with etanercept 50 mg once weekly; however, patients in the second arm who had responded to treatment (defined as PGA ≤ 2 and improvement from baseline) discontinued treatment and were reinitiated only upon relapse (defined as loss of responder status) at week 16 or 20. Efficacy analysis at week 24 showed a PGA ≤ 2 for 70% of the patients in the continuous group and a PGA ≤ 2 for 51% of the patients in the interrupted group. In the latter group, median time to relapse was 39.6 days and median time to regain responder status after retreatment was 35.0 days [146].

The significant improvement in PASI scores seen in the abovementioned study by Leonardi et al was accompanied by an improvement in the global assessment by the physician. In addition, the Dermatology Quality of Life Index (DLQI) improved by 50.8% (25 mg biweekly) and 61% (50 mg biweekly) among the etanercept treated patients [149]. Similarly, the abovementioned study by Cassano et al (grade of evidence B) demonstrated a mean improvement of 68% on the DLQI and of 69% on a visual analogue scale for pruritus after 12 weeks of treatment with etanercept 50 mg biweekly; the mean improvement of these scores in the etanercept 100 mg weekly group was comparable (i.e. 66% and 72%, respectively) [152].

Adverse drug reactions/safety

Etanercept appears to be a relatively safe drug in the short term. The risk of organ failure, such as renal or liver dysfunction, is rare in associated with its use. In the last decade, etanercept has been employed in large number of patients with rheumatoid arthritis and inflammatory bowel disease. It appears to be safe in this population, but well-designed post-marketing safety studies are lacking [155]. A recent study that followed up 464 patients for 96 weeks showed no increase in the incidence of malignancies or infections among psoriasis patients treated with etanercept compared to patients receiving placebo and/or to the general population [153] (see special considerations).

Table 28: Overview of important side effects

Very frequent	Injection-site reactions, infections (upper respiratory tract, bronchitis, skin infections)
Frequent	Pruritus
Occasional	Thrombocytopenia, urticaria, angioedema, severe infections (pneumonia, cellulitis, sepsis), weight gain
Rare	Anaemia, leucopenia, neutropenia, pancytopenia, vasculitis, subacute and discoid lupus erythematodes, demyelinating disease, tuberculosis
Very rare	Aplastic anaemia

Important contraindications/restrictions on use

Absolute contraindications

- Pregnancy/breastfeeding
- Active (chronic) infections (including tuberculosis and active chronic hepatitis B)
- Congestive heart failure (NYHA grade III or IV)

Relative contraindications

- PUVA >200 treatments (especially if followed by ciclosporin use)
- HIV or AIDS
- Hepatitis C
- Congestive heart failure (NYHA grade I or II)
- Demyelinating disease
- Malignancies or lymphoproliferative disorders
- Live vaccines

Drug interactions

For important drug interactions see Table 29, page 74. Live-attenuated vaccines should not be administered during treatment with any of the biologic agents. Depending on their half-life, biologics should be discontinued four to eight weeks prior to an immunization and may be restarted two to three weeks later.

Table 29: List of most important drugs with potential interactions

Drug	Type of interaction
Anakinra	Neutropenia and serious infections
Immunosuppressive drugs (ciclosporin, MTX, other biologicals)	Increased immunosuppression
PUVA	Skin cancer risk

Instructions for use

Necessary measures
Due to the lack of long-term data, the guidelines development group feels that caution is advisable and monitoring during treatment should be performed. <u>Pre-treatment</u> • Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • History and clinical examination should focus on prior exposure to treatments, malignancies, infection, congestive heart failure, and neurological symptoms • Recommended measures include: – Check for skin cancer – Check for lymphadenopathy – Laboratory parameters (see Table 30, page 75) – Urine analysis – Chest X-ray – Mantoux test and/or QuantiFERON®-TB Gold test® test – In case of doubt, contact a specialist – Pregnancy test

- Contraception

During treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL such as (DLQI/Skindex-29 or -17)
- Clinical examination should focus on malignancies, risk factors for serious infections, congestive heart failure, and neurological symptoms
- Recommended measures include:
  - Check for skin cancer
  - Check for lymphadenopathy
  - Laboratory parameters (see Table 30, page75)
  - Urine analysis
- Contraception

Post-treatment

- After discontinuation of etanercept, patients should be followed up with medical history and physical examination
- Physicians are encouraged to enrol their patients in a registry (if available)

Overdose/measures in case of overdose

No dose-limited toxicity was observed in clinical trials with patients suffering from rheumatoid arthritis. Intravenous administration of 32 mg/m² was the highest examined dose, followed by subcutaneous injections of 16 mg/m² twice weekly. There is no known antidote for etanercept [156].

Table 30: Lab controls

	Period in weeks			
Parameter	Pre-treatment	4	12	Thereafter, every 3 months
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x	x	x	x

Urine sediment	x	x	x	x
Pregnancy test (urine)	x	x	x	x
Sed rate/CRP	x	x	x	x
HBV and HCV	x			
HIV	x			
Further specific testing may be required according to clinical signs, risk, and exposure.				

Special considerations

Discontinuation of etanercept

After long-term control (i.e. PASI 75) has been achieved, etanercept can be discontinued. Open-label studies show sustained efficacy over time, with no evidence of loss of efficacy with interrupted therapy. Time to relapse (loss of 50% of PASI improvement) after discontinuation is between 70 to 90 days and seems slightly longer for the 50 mg biweekly dosage. The difference between tapering the dose of etanercept and discontinuing the drug abruptly has not been studied, and tapering is not recommended because of the low risk of relaps.

Infections

Screening for serious infection during therapy is indicated and should include a patient history, physical examination including lymphadenopathy, leucocytosis, erythrocyte sedimentation rate (i.e. sed rate), CRP, and urine analysis according to the instructions for use table, page 74. An infection is considered severe if oral antibiotics are warranted.

TBC and TBC screening

Potential recipients of TNF antagonists should be rigorously screened with skin testing, detailed questioning about potential tuberculosis exposure (including recent travel), assessment for symptoms such as cough and weight loss, and chest radiography (see instructions for use table, page 74). A Mantoux test and/or QuantiFERON®-TB Gold test® should be performed at baseline. Use of the QuantiFERON®-TB Gold test® is suggested in patients whose Mantoux test result is uncertain. The tuberculin skin test (TST) is the current gold standard, but has several limitations, including the need for two visits to the clinic (intradermal injection and 48 to 72 hours later); a sensitivity and specificity of 74% and 81%, respectively; its being subject to interrater variability; difficulty in interpreting results in

patients who have received BCG vaccination in the past; potential unreliability in patients on an immunosuppressive therapy; false positive results in approximately a quarter of cases [142]. The QuantiFERON®-TB Gold test® may be the future gold standard in TBC testing [142]. Approved by the FDA for the diagnosis of latent and chronic tuberculosis in 2005, the test detects IFN-gamma release by TBC antigen-sensitized white blood cells. Its sensitivity is 89% and specificity 98.1%. Each test costs approximately US $200.

Corresponding monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy. Particular care should be taken when patients come from areas where certain opportunistic infections are endemic. As with other immunosuppressive drugs, TNF antagonists should not be given to patients with active infections. If latent tuberculosis is suspected, etanercept therapy may be initiated in combination with prophylactic treatment, preferably isoniazid, started one month before etanercept therapy and continued for nine months.

Hepatitis/HIV

Although not mandatory, testing for HIV and hepatitis B and C infection is desirable, especially in patients who are at higher risk. Because of the risk of reactivation, chronic carriers of hepatitis B should not be treated with etanercept. Patients with hepatitis C should be appropriately evaluated and monitored during etanercept therapy.

Malignancies, including lymphoma

Although it is presently unknown whether psoriasis patients treated with TNF antagonists have a higher risk of lymphoma or skin cancer, a potential risk for the development of lymphoma or other malignant diseases cannot be excluded based on current knowledge. It should be noted, however, that patients with psoriasis, similar to patients with rheumatoid arthritis, have a higher baseline lymphoma risk compared to the general population [143] and may also carry an increased risk of developing skin cancer due to previous UV phototherapy, particularly PUVA, or to the use of immunosuppressive drugs, such as ciclosporin [95, 96]. Therefore all patients, particularly those with intensive immunosuppressive therapy in their medical history, as well as psoriasis patients with prior PUVA therapy, should be evaluated for non-melanoma skin cancer, both before and during TNF-antagonist therapy.

Other safety aspects

As a class, TNF blockers may be associated with the development or worsening of demyelinating diseases and multiple sclerosis. Infliximab and etanercept have been known to

worsen pre-existing heart failure. TNF blockers are contraindicated in patients with severe heart failure (NYHA grade III or IV), and patients with less severe disease should be monitored carefully and undergo cardiology consultations every three months. Although ANA and, to a lesser extent, ds-DNA antibodies may develop during the use of TNF antagonists (between 10% and 70% for etanercept in patients with rheumatoid arthritis and 18% in psoriasis patients [153]), they are often transient IgM responses and disappear after discontinuation of therapy; drug-induced lupus erythematodes is rare. Because only about 5% of patients treated with etanercept develop antibodies and the relevance of these antibodies is unclear, it is not likely that MTX can prevent "loss of efficacy."

Combination therapy

Table 31: Possibilities for therapeutic combination

	Recommendation	Comments
Methotrexate	+/-	Under investigation in psoriasis, but common in rheumatology
Ciclosporin	--	Increased immunosuppression
Retinoids	+	One RCT showing similar efficacy for acitretin in combination with 1 x 25 mg etanercept versus 2 x 25 mg etanercept [122]
Fumaric acid esters	-	Caution for lymphopenia
Biologics	-	Increased immunosuppression
Phototherapy	--	Skin cancer risk may be increased, especially in PUVA-treated patients.

Summary

A total of eight studies fulfilled the criteria for inclusion in the guidelines. Etanercept is effective in the treatment of moderate to severe plaque psoriasis, with approximately 49% of patients achieving a PASI 75 response with 50 mg twice weekly, and approximately 33% of patients achieving a PASI 75 response with 25 mg twice weekly, by week 12 (level of evidence 1). In about 50% of patients, etanercept is effective in achieving a substantial psoriasis clearance within 24 weeks. Monitoring of (potential) users of etanercept focuses primarily on infections and the development of cancer. Interactions with other drugs are

limited, except for increased immunosuppression caused by use of some drugs. Injection-site reactions are the most common adverse event. Etanercept may also increase the risk of (serious) infections, including reactivation of tuberculosis. The long-term safety of etanercept, including the risk of haematological and solid malignancies, is not well studied in psoriasis patients.

Therapeutic recommendations

- Etanercept is suggested for induction therapy (25 mg or 50 mg biweekly) for moderate to severe psoriasis if photo(chemo)therapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated.
- If, after 10 to 16 weeks, induction therapy is considered successful, maintenance therapy can be considered with the lowest effective dose.

3.7 Infliximab

Reich/Kemeny

Introduction/general information

Infliximab (Remicade®) is a monoclonal antibody and member of the so-called TNF antagonists. It binds with high affinity, avidity, and specificity to TNF-α and, through its inhibitory, neutralizing, and cytotoxic activity, interferes with the pathomechanism of psoriasis and other inflammatory diseases that are characterized by TNF overproduction.

Infliximab is a chimeric antibody. The variable regions are of murine origin and are coupled to human IgG_1 and kappa constant domains. Like other biologics, infliximab is classified as part of the pharmacotherapeutic group of selective immunosuppressive agents (ATC Code: L04AA12). It is a member of the class of disease-modifying antirheumatic drugs (DMARDs), which are used for targeted modulation of chronic inflammatory reactions.

Table 32: Tabular summary

Infliximab	
Approval for psoriasis	September 2005 (EMEA)
Recommended controls	Full blood count, liver enzymes, ESR/CRP,

	creatinine, urine analysis, pregnancy test (urine), HBV/HCV, HIV (prior to therapy), screening for tuberculosis including chest X-ray (prior to therapy)
Recommended initial dose	5 mg/kg body weight
Recommended maintenance dose	5 mg/kg body weight 2, 6, and then every 8 weeks thereafter.
Clinically significant response expected after	1-2 weeks
Response rate	PASI 75 in approximately 80% of patients after 10 weeks
Absolute contraindications	Active tuberculosis; significant active infection; heart failure (NYHA III/IV); chronic hepatitis B; hypersensitivity to infliximab, murine proteins, or any component of the formulation
Important side effects	Infusion reaction; severe infections; worsening of severe congestive heart failure (NYHA III/IV); autoimmune events (lupus erythematodes syndrome)
Important drug interactions	None
Special considerations	Reliable contraception until 6 months after end of treatment in women of childbearing potential required

Mechanism of action

Increased levels of TNF-α are detectable in active skin and joint lesions of psoriasis and in the serum of affected patients [157, 158]. In vitro data and recent animal models suggest that TNF-α may play a part early in the initial manifestation of psoriasis [159-162], as well as orchestrate a variety of secondary events that contribute to the perpetuation of the disease process. By antagonizing TNF-α and possibly by depleting TNF-α-producing cells, infliximab is believed to decrease (a) the upregulation of adhesion molecules on endothelial cells and the vascular changes seen in psoriasis, (b) the release of pro-inflammatory cytokines from antigen-presenting cells and T cells, (c) the increased and aberrant proliferation of keratinocytes, and (d) the promotion of synovial tissue damage [160-162].

TNF-α is detectable as a soluble cytokine, which is usually active as a homotrimer, and is also found as a monomer, dimer, and trimer on the surface of TNF-α-producing cells. Infliximab binds all forms of soluble and membrane-bound TNF-α with high specificity, but unlike the TNF antagonistic fusion protein etanercept, it does not bind lymphotoxin (TNF-β).

Infliximab and TNF are multivalent. It has been shown that, in antigen excess, one infliximab molecule can bind two different TNF trimers, whereas in antibody excess, three infliximab molecules can bind to one TNF trimer. The high affinity due to the formation of large immune complexes, which is referred to as avidity, significantly reduces the possibility that bioactive TNF can dissociate from infliximab. The ability of infliximab to bind to membrane-bound TNF-α with high avidity might account for some of the drug's cell-depleting effects (apoptosis, complement lysis, antibody-dependent cellular cytotoxicity), which have been described in vitro [163] and in vivo [164] and postulated to contribute to the clinical effects of infliximab [165]. There is also evidence that the relevance of infliximab-mediated apoptosis as part of the mechanisms underlying its clinical effects may vary between different diseases. More recent findings in rheumatoid arthritis indicate a reduction of the synovial cell infiltrate independent of cell death [166].

Dosing regimen

Infliximab is supplied as a freeze-dried powder in 100 mg vials. The powder should be stored at a temperature between 2°C and 8°C. After reconstitution of the powder in 10 mL of sterile water/bottle, the appropriate total dose of infliximab is diluted with 250 mL of a 0.9% saline solution and infused using a filter system. The drug should be infused preferably within three hours after reconstitution of the powder and no later than 24 hours after interim storage between 2°C and 8°C.

Infliximab is administered as a short intravenous infusion over a period of two hours at a total dose of 5 mg/kg body weight per infusion. According to the label for plaque-type psoriasis, therapy is started with infusions at weeks 0, 2, and 6, which can be regarded as an induction regimen, and then continued every 8 weeks thereafter for maintenance therapy. Other doses or treatment intervals are currently not recommended for this indication.

Efficacy

Six clinical trials were identified that fulfilled the criteria for inclusion in the guidelines [167-172]; three were assigned a grade of evidence of A2, one a grade of evidence of B, and two a grade of evidence of C. The overall level of evidence was classified as 1. Five trials included primarily patients with plaque-type psoriasis and determined clinical efficacy at week 10 (three infusions); one study additionally reported on the efficacy at week 50 (eight infusions) in a larger patient population. One of the included studies investigated the effect of infliximab

in psoriatic arthritis, and also assessed the clinical effect on psoriatic skin symptoms at week 22.

In a double-blind, placebo-controlled pilot study in 33 patients (grade of evidence B), 82% of patients receiving 5 mg/kg achieved a PASI 75 response at week 10 compared to 18% in the placebo group [168]. Three infusions at a higher dose of 10 mg/kg body weight did not lead to improved clinical efficacy. In another trial (grade of evidence A2), 249 patients received induction therapy with placebo, or infliximab at a dose of 3 mg/kg or 5 mg/kg body weight [169]. At week 10, 88% of patients treated with 5 mg/kg achieved PASI 75 compared with 72% of patients treated with 3 mg/kg dose and with 6% of patients receiving placebo. A PASI 90 response at week 10 was seen in 58% of patients in the 5 mg/kg dose group (3 mg/kg body weight: 46%; placebo: 2%). At week 26 of the study, 20 weeks after the last infusion, 33% of patients in the 5 mg/kg group still had a PASI 75 response (placebo: 6%). In a phase III maintenance trial over one year (grade of evidence A2), 301 patients received induction therapy with infliximab at 5 mg/kg and continued with subsequent infusions every eight weeks until week 46 [170]. In week 24, patients in the placebo group (n = 77) were crossed over to receive infliximab 5 mg/kg induction and maintenance therapy. In total, 80% of patients treated with infliximab achieved PASI 75 at week 10 compared to 3% in the placebo group. A PASI 90 response was achieved by 57% of infliximab-treated patients at week 10 compared to 1% in the placebo group, and 26% of the patients treated with infliximab were free of psoriatic skin symptoms (PASI 100). At week 50, based on all available datasets (n = 281), 61% of patients in the infliximab group had a PASI 75 response and 73.6% of patients with PASI 75 at week 10 had maintained their response through week 50. This study also demonstrated a significant improvement of nail psoriasis, although the improvement occurred more slowly than the improvement shown for skin symptoms.

PASI 75 responses at week 10 in approximately 80% of patients treated with infliximab were also seen in two smaller studies [171, 172] with 8 and 23 patients, respectively (grade of evidence C). In a study of psoriatic arthritis [167], PASI 75 and PASI 90 responses at week 22 were 64% (placebo: 2%) and 41% (placebo: 0%), respectively. However, these results are difficult to compare to the results obtained in the other studies due to the different patient populations included.

Overall, a PASI 75 response at week 10 was achieved by 77% to 88% of patients treated with the labelled dose of 5 mg/kg body weight in studies on plaque-type psoriasis, and approximately 75% of patients maintained this response over one year of treatment [170]. A

PASI reduction of 50%, which can be regarded as a clinically meaningful response, was observed within approximately two to five weeks of treatment. At least two large studies also demonstrated a significant improvement in quality of life parameters among patients treated with infliximab, such as the DLQI [173, 174]; productivity parameters also improved with treatment [175].

Adverse drug reactions/safety

Due to its use in a variety of indications, including rheumatoid and psoriatic arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriasis, infliximab has become the most commonly employed TNF antagonist to date, with more than 10 years of patient exposure and safety data. As of August 2005, the estimated patient exposure since the commercial launch of the drug in August 1998 is 698 486 patients, corresponding to an estimated 1 909 941 patient-years; these figures are based primarily on the use of infliximab in rheumatoid arthritis, spondyloarthropathies, and Crohn's disease. The overall safety profile of infliximab appears to be similar for all of the different indications. However, at present there is insufficient long-term data on the safety of infliximab in patients with plaque-type psoriasis.

Key safety considerations for infliximab include common side effects (mainly infections and infusion reactions), as well as rare but important side effects, such as opportunistic infections, particularly tuberculosis. The relationship between infliximab and some other significant events that have been observed infrequently during treatment, including cases of severe liver toxicity, demyelinating diseases, or lymphoma, is less clear and therefore increased caution is recommended. An overview of important side effects associated with infliximab is given in the Table 33.

Table 33: Overview of important side effects

Very frequent	Infusion reactions
Frequent	Infections, headache, flush, pruritus, urticaria, fever, transaminase elevation
Occasional	Serum-sickness-like disease, (cutaneous) lupus erythematodes syndrome, severe infections, tuberculosis, anaphylactoid reaction
Rare	Opportunistic infections, pancytopenia, vasculitis, demyelinating diseases
Very rare	

Infusion reactions

In clinical trials, infusion reactions (defined as any adverse events occurring during or within one hour after completion of the infusion) were the most common reasons for discontinuation of therapy. Infusion reactions were seen in approximately 20% of infliximab-treated patients in all clinical trials as opposed to approximately 10% of patients receiving placebo. Most of these infusion reactions are mild to moderate, including symptoms such as flush, pruritus, chills, headache, and urticaria. Severe infusion reactions, such as anaphylactic reactions, as well as serum-sickness-like delayed-type hypersensitivity reactions (myalgia, arthralgia and/or exanthema occurring between 1 and 14 days after infusion) occur in ~1% of patients. Infusion reactions tended to be less common in clinical trials on plaque-type psoriasis, where they were reported in approximately 10% of patients receiving infliximab. The percentage of patients who develop antibodies to infliximab is approximately 10% to 30%. Patients who develop antibodies to infliximab appear to have an increased risk of infusion reactions [176].

If mild to moderate infusion reactions occur, treatment can usually be continued after decreasing the infusion rate or temporarily stopping the infusion. In these cases, pre-treatment with oral antihistamines, paracetamol/acetaminophen, and/or glucocorticosteroids should be considered for future infusions.

Infections

Infections are the most common adverse event described in spontaneous post-launch reports. Infliximab has also been associated with the occurrence of severe infections, including in rare cases life-threatening events, such as sepsis. In all completed clinical trials with infliximab, 36.4% of patients in the placebo groups (n = 1600; average weeks of follow-up: 29.0) and 52.0% of patients in the infliximab groups (n = 5706; average weeks of follow-up: 45.5) experienced more than one infection [177]. Serious infections were seen in 2.0% of placebo-treated and in 4.0% of infliximab-treated patients, the difference being due mainly to a higher rate of pneumonia and abscesses among patients receiving infliximab. Patients receiving infliximab are at an increased risk of reactivation or exacerbation of granulomatous infections, in particular tuberculosis. Many cases of tuberculosis associated with infliximab occurred in geographic areas where tuberculosis is endemic and following the first few infusions, indicating a possible reactivation of latent tuberculosis (see also special considerations) [178]. The majority of patients experienced extrapulmonary tuberculosis (57%), and almost 25% of these patients had disseminated disease.

Histoplasmosis, listeriosis, aspergillosis, coccidioidomycosis, and candidiasis have also been associated with TNF antagonists, but the causative relationship is not clear [179].

Antinuclear antibodies and skin symptoms reminiscent of cutaneous lupus erythematosus

Up to 50% or more of patients treated with infliximab may develop antinuclear antibodies that are frequently of transient nature. Many of the recorded patients suffer from conditions such as rheumatoid arthritis that predispose to the development of ANAs. In addition, *de novo* formation of anti-dsDNA antibodies occurred in approximately 17% of infliximab patients in clinical trials, but not in patients receiving placebo. These autoantibodies are usually of low titre and mostly not associated with clinical symptoms. Treatment can be continued in patients with newly developed ANA without associated symptoms. The formation of autoantibodies has been associated in less than 1% of cases with the onset of symptoms reminiscent of lupus erythematosus, which are almost always confined to the skin. In such patients it is recommended to discontinue infliximab treatment.

Elevated liver enzymes

In clinical studies with infliximab in plaque-type psoriasis, up to 8% of patients developed markedly elevated aspartate and alanine aminotransaminase levels (>150 U/l and more than twice from baseline) [170], an event that has been seen less frequently in clinical trials for other indications. The elevation of liver enzymes occurred independently of a reactivation of viral hepatitis and was usually not associated with other abnormalities indicative of liver function impairment (e.g. abnormal bilirubin levels). Treatment can be continued in the majority of cases with close monitoring. However, rarely, a more severe hepatopathy may occur; a respective warning has been issued recently in the U.S. product information. Reactivation of hepatitis B may occur in patients receiving infliximab who are chronic carriers of this virus (i.e. surface antigen positive).

The following guidelines are used in clinical trials with respect to the elevation of aminotransferases: treatment possible if values <3 × upper limit of normal (ULN); treatment with caution if values 3 to 5 × ULN; stop treatment if values >5 × ULN.

Malignancies, including lymphoma

In clinical trials in different indications, the observed malignancy rate (lymphoma and non-lymphoma) was lower in control than in infliximab-treated patients, but the latter did not exceed the rates expected for the general population according to the Surveillance,

Epidemiology and End Results (SEER) database of the U.S. National Cancer Institute. In the EXPRESS phase III trial in psoriasis, three patients (1%) with non-melanocytic skin tumours were reported in the infliximab group, compared to none among the placebo-treated patients [170]. In clinical trials for different indications, lymphomas were observed more frequently in patients receiving infliximab than in subjects on placebo. Most lymphomas associated with TNF antagonists are non-Hodgkin's lymphomas, with a mean time to onset of 10 to 21 months. It should be noted that, in clinical trials, patients on placebo usually had a shorter time of follow-up than patients treated with active drug. In registries for rheumatoid arthritis, lymphomas were observed more frequently in patients treated with TNF antagonists than in the general population. Lymphomas were also observed more frequently in rheumatoid arthritis patients receiving standard disease-modifying antirheumatic drugs. In patients with Crohn's disease treated with infliximab or adalimumab, a rare variant of aggressive hepatosplenic lymphoma has been observed. Similar types of lymphoma have also been observed in patients treated with azathioprine or 6-mercaptopurine. The majority of patients who developed hepatosplenic lymphoma during treatment with TNF antagonists had also been treated or were treated concomitantly with azathioprine or 6-mercaptopurine. The overall reporting rates for lymphomas from post-marketing experience with TNF antagonists (0.02-0.03 events per 100 patient-years) do not indicate an increased risk when compared to the expected rate of lymphomas from the SEER database (0.07 events per 100 patient-years in a 65-year-old population) [180].

Although it is presently unknown whether psoriasis patients treated with TNF antagonists have a higher risk of lymphoma or skin cancer, a potential risk for the development of lymphoma or other malignant diseases cannot be excluded based on current knowledge. It should be noted, however, that patients with psoriasis, similar to patients with rheumatoid arthritis, have a higher baseline lymphoma risk compared to the general population [143] and may also carry an increased risk of developing skin cancer due to previous UV phototherapy, particularly PUVA, and to the use of immunosuppressive drugs, such as ciclosporin [95, 96]. As a result, all patients, particularly those with an intensive immunosuppressive therapy in their medical history, as well as psoriasis patients with prior PUVA therapy, should be evaluated for non-melanoma skin cancer both before and during TNF antagonist therapy.

Pregnancy and breastfeeding

Administration of infliximab is not recommended during pregnancy or breastfeeding (FDA pregnancy category B). Because of the long half-life of the product, reliable contraception is

required in women of child-bearing potential until six months after the last infusion. In a preclinical developmental toxicity study conducted in mice, there was no evidence of maternal toxicity, embryotoxicity, or teratogenicity. In a recent retrospective survey of 131 women with Crohn's disease directly exposed to infliximab, no significantly increased adverse outcomes following exposure to infliximab shortly before conception or during pregnancy were observed [181].

If a patient becomes pregnant during infliximab therapy, the treatment should be stopped. However, since available data indicate no increased risk for miscarriage or foetal abnormalities, there is no medical indication to terminate the pregnancy.

Other safety aspects

Because of reports on the new onset or exacerbation of multiple sclerosis under anti-TNF therapy, which are reversible after discontinuation of treatment (reviewed in [182]), infliximab should not be given in patients with a history of multiple sclerosis or other types of demyelinating disease. In addition, patients with severe congestive heart failure (CHF) (NYHA class III-IV) who receive high doses of TNF antagonists have an increased risk of worsening of CHF [183]. Therefore, anti-TNF agents including infliximab should not be administered to these patients. In patients with milder forms of CHF, infliximab can only be used after consideration of other therapeutic options and with vigilant monitoring of the patients. Therapy should be discontinued if new symptoms occur or if CHF symptoms worsen.

Important contraindications/restrictions on use

Absolute contraindications

- Active tuberculosis
- Significant active infection
- Active chronic hepatitis B
- Heart failure (NYHA III/IV)
- Hypersensitivity to infliximab, murine proteins or any component of the formulation
- Pregnancy or breastfeeding

Relative contraindications

– Demyelinating diseases

– Live vaccines

- PUVA >200 treatments (especially if followed by ciclosporin use)
- Malignancies or lymphoproliferative disorders
- Hepatobiliary disorders
- Hepatitis C

Drug interactions

There are no known interactions of infliximab with the metabolism of other drugs. A single infusion of infliximab leads to a mean maximum serum concentration of 118 µg/mL. The mean elimination half-life is ~8.5 to 9 days; however, depending on the dose and duration of treatment, infliximab can be detected in the serum for up to 28 weeks. The combination of infliximab with immunosuppressive drugs may enhance the risk of infection. The combination with low-dose methotrexate (7.5 to 10 mg weekly) is often used in the treatment of rheumatologic indications and seems to improve the long-term efficacy of infliximab. To date, there is no indication that the safety profile of this combination is less favourable than that of infliximab monotherapy. The combination with PUVA therapy might enhance the risk for skin cancer development. Live-attenuated vaccines should not be administered during treatment with any of the biologic agents. Depending on their half-life, biologics should be discontinued four to eight weeks prior to an immunization and may be restarted two to three weeks later.

Instructions for use

Necessary measures
Due to the lack of long-term data, the guidelines development group feels that caution is advisable and monitoring during treatment should be performed. <u>Pre-treatment</u> • Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • History focusing on prior exposure to treatments. History and clinical examination should focus on malignancies, infection, congestive heart failure, and neurological symptoms • Recommended measures include: – Check for skin cancer

  - Check for lymphoadenopathy
  - Laboratory parameters (see Table 34, page 90)
  - Urine analysis
  - Chest X-ray
  - Mantoux test and/or QuantiFERON®-TB Gold test® test
  - In case of doubt, contact a specialist
  - Pregnancy test
- Contraception

During treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/ Skindex-29 or -17)
- Clinical examination should focus on malignancies, risk factors for serious infections, congestive heart failure, and neurological symptoms
- Recommended measures include:
  - Check for skin cancer
  - Check for lymphoadenopathy
  - Laboratory parameters (see Table 34, page 90)
  - Urine analysis
- Contraception

Post-treatment

- After discontinuation of infliximab, patients should be followed up with medical history and physical examination
- Physicians are encouraged to enrol their patients in a registry (if available)

Overdose/measures in case of overdose

The dose of infliximab should be calculated individually based on the weight of the patient. In case of overdose, the patient should be followed closely for adverse events, particularly infections. Dosing intervals during induction therapy should follow the recommended regimen, and during maintenance therapy should generally not be shorter than four weeks.

Table 34: Lab controls

	Period in weeks			
Parameter	Pre-treatment	2	6	Thereafter, prior to each infusion
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Creatinine	x	x	x	x
Urine analysis	x	x	x	x
Pregnancy test (urine)	x	x	x	x
ESR/CRP	x	x	x	x
HBV/HCV	x			
HIV	x			
Further specific testing may be required according to clinical signs, risk, and exposure.				

Special considerations

TBC and TBC screening

Potential recipients of infliximab and other TNF antagonists should be rigorously screened with skin testing, detailed questioning about potential tuberculosis exposure (including recent travel), assessment for symptoms such as cough and weight loss, and chest radiography (see instructions for use table, page 88). Corresponding monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy. Particular care should be taken when patients come from areas where certain opportunistic infections are endemic. As with other immunosuppressive drugs, TNF antagonists should not be given to patients with active infections. The value of screening measures has become apparent from the reduction of reported tuberculosis cases in patients receiving infliximab after initiation of a tuberculosis education and screening programme, with the reporting rate per 1000 exposed patients dropping from approximately 1.5 as of June 2001 to 0.6 by August 2005.

In recent years, two novel tests for tuberculosis have become available: the QuantiFERON®-TB Gold test [184] and the ELISPOT-based T-Spot®.TB. The QuantiFERON®-TB Gold test and the T-Spot®.TB measure the production of IFN-γ after stimulation with antigens present in *M.*

tuberculosis in whole blood and in isolated peripheral blood mononuclear cells, respectively. Both tests produce results within 24 hours. They offer the advantage over the tuberculin skin test that they appear not to be affected by prior bacille Calmette-Guérin (BCG) vaccination or by infection with commonly encountered non-tuberculous mycobacteria. If latent tuberculosis is suspected, infliximab therapy may be initiated in combination with prophylactic treatment, preferably isoniazid, started one month before infliximab therapy and continued for nine months. Presence of active tuberculosis is an absolute contraindication for therapy with TNF antagonists. Recommendations for the screening, diagnosis, and treatment of tuberculosis in patients scheduled to receive or receiving TNF-blocking agents are, for example, available from the U.S. Centers for Disease Control and Prevention [185].

Hepatitis/HIV

Although not mandatory, testing for HIV and hepatitis B and C infection is desirable, especially in patients who are at higher risk. Because of the risk of reactivation, chronic carriers of hepatitis B should not be treated with infliximab. Patients with hepatitis C should be appropriately evaluated and monitored during infliximab therapy.

Combination therapy

The combination of infliximab with other therapies has not been formally investigated in clinical trials. Infliximab is usually combined with topical therapies, such as corticosteroids or vitamin D3 analogues, according to clinical requirements. Although infliximab is often used in combination with methotrexate in rheumatologic conditions, including psoriatic arthritis, this combination has not been systematically investigated in chronic plaque psoriasis, and the label for this indication specifies that infliximab should be used as monotherapy. There is, however, increasing evidence that a subgroup of patients with psoriasis in whom therapeutic infliximab serum levels are not maintained over time might also benefit from the combination with low-dose methotrexate, which probably reduces the incidence of antibody development.

In summary, the combination of infliximab with other systemic antipsoriatic agents is currently not recommended, except for the combination with low-dose methotrexate, particularly for the long-term treatment of patients with severe chronic psoriasis or patients with associated significant psoriatic arthritis.

Because the effect of infliximab on the development of skin malignancies is unknown, the combination with phototherapy should be avoided.

Table 35: Possibilities for therapeutic combination

	Recommendation	Comments
Methotrexate	+/-	Under investigation in psoriasis, but common in rheumatology
Ciclosporin	-	Increased immunosuppression
Retinoids	+/-	Preliminary positive experience with etanercept
Fumaric acid esters	-	Lack of experience
Biologics	-	Increased immunosuppression
Phototherapy	-	Increased risk of skin cancer possible

Summary

Six clinical trials were identified that fulfilled the criteria for inclusion in the guidelines. Infliximab is highly effective in the treatment of moderate to severe plaque psoriasis, with approximately 80% of treated patients achieving a PASI 75 response and more than 50% achieving a PASI 90 response at week 10 (level of evidence 1). The majority of patients maintain the clinical response over at least one year of therapy and possibly longer, as indicated in studies in psoriatic arthritis. The effect on skin symptoms is associated with significant improvements in quality of life and productivity. In a small subgroup of approximately 10% to 20% of patients, the initial response is lost, presumably due to decreasing infliximab serum levels. These patients may benefit from combination therapy with low-dose methotrexate. Important side effects associated with infliximab include infections and infusion reactions.

Therapeutic recommendations

- Infliximab is recommended for induction therapy for moderate to severe psoriasis if photo(chemo)therapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated.
- The advantage of this drug is its rapid and marked clinical efficacy.
- If, after 10 to 16 weeks, induction therapy is considered successful, maintenance therapy can be considered.

3.8 Ustekinumab

Ustekinumab has been registered for systemic treatment of moderate to severe psoriasis in 2009 [186]. A formal evaluation is not included in these guidelines because of the deadline of literature research being prior to the registration of ustekinumab but will be given in the next guideline update.

3.9 Alefacept

Menter

Introduction/general information

Alefacept, a recombinant human LFA-3 IgG1 fusion protein, was the first biologic agent approved in the United States for chronic plaque psoriasis (January 2003). In Europe it was approved in Switzerland in 2004. Activation of effector memory T cells is inhibited when alefacept binds to CD2, with a remittive effect in a small percentage of patients following a prescribed 12-week treatment course.

Table 36: Tabular summary

Alefacept	
Approval for psoriasis	2004 (Switzerland)
Recommended controls	Blood count, liver enzymes, ESR/CRP, serum creatinine, urine sediment, pregnancy test (urine), CD4+ T-cell monitoring, HBV/HCV, HIV (prior to therapy)
Recommended initial dose	12 weeks at 15 mg weekly intramuscular injections
Recommended maintenance dose	12 weeks at 15 mg weekly intramuscular injections with minimum of 12-week intervals

	between courses
Clinically significant response expected after	2-6 weeks following a 12-week course
Response rate	PASI 75 in 21% at 14 weeks
Absolute contraindications	Systemic malignancy, HIV infection, reduced T-cell count, active chronic hepatitis B, hypersensitivity to alefacept component
Important side effects	Lymphopenia (CD4+ T cells), malignancies, serious infections, allergic reactions, hepatic injury
Important drug interactions	None
Special considerations	Slow initial response; subsequent course improves responses. Lengthy remissions in subgroup of patients

Mechanism of action

Alefacept's dual mechanism of action involves:

1) inhibition of T-cell activation and proliferation by binding to the CD2 receptor on T lymphocytes, thereby blocking LFA-3 and CD2 interaction
2) T-cell apoptosis, resulting in selective reduction in effector memory T cells and, hence, modification of the inflammatory process in psoriasis

Dosing regimen

Alefacept should be given at a dose of 15 mg intramuscularly once weekly for 12 weeks.

Multiple subsequent 12-week courses are possible in responders, with a minimum interval of 12 weeks between these courses.

Efficacy

Of the six studies that fulfilled the criteria for inclusion in the guidelines, five investigated alefacept monotherapy. Two of these were assigned a grade of evidence of A2 [187, 188], two a grade of evidence of B [189, 190], and one with a grade of evidence of C [191]. The overall level of evidence was classified as 1. One additional study, with a grade of evidence of B, was included for the assessment of combination therapy with UVB [192].

Two studies with a weekly dose of 7.5 mg (or 0.075 mg/kg) intravenous alefacept demonstrated a PASI 75 or PASI 50 response within 12 weeks in 33% or 60% of patients [187] or in 14% to 38% of patients [188] with moderate to severe plaque psoriasis (both studies: grade

of evidence A2). A retreatment study of patients who had been treated previously with alefacept at different doses demonstrated a PASI 75 for 39% of patients within 14 days for the same dose (grade of evidence C) [191].

A similar treatment effect with a documented PASI 75 in 21% to 31% of patients was shown by Ortonne et al (grade of evidence B) [190] and Ellis et al (grade of evidence A2) [187] for treatment with 15 mg once weekly; it should be noted that alefacept was administered intramuscularly in the first study. A poorer therapeutic effect was shown with a dose of 0.025/kg BW administered intravenously in the study by Ellis et al [187].

Two studies evaluated the treatment effect after a follow-up period of 12 weeks after last treatment with alefacept [187, 190]. Ellis et al (grade of evidence A2) demonstrated that the clinical improvement was sustained 12 weeks after therapy with 0.075 mg/kg intravenous alefacept, with 31% of patients showing a PASI 75 at this point. In the same study, 19% of patients receiving 0.15 mg/kg BW intravenous alefacept demonstrated a PASI 75. Ortonne et al (grade of evidence B) found 33% of patients with a PASI 75 within 12 weeks after treatment with 15 mg of intramuscular alefacept once weekly.

In addition to the PASI improvement, Ellis et al showed that 16% of patients who completed the 12-week alefacept treatment regime were considered clear or almost clear of psoriasis. In the study by Ortonne et al, 24% of patients achieved this PGA within 24 weeks [190].

Krueger et al showed a continuous PASI improvement for patients who received two courses of alefacept treatment with a follow up of 12 weeks after each treatment; nearly one third of these patients were clear or almost clear on the PGA, and more than two thirds achieved a PASI 50. Furthermore, Krueger et al showed that patients who had achieved a PGA of clear or almost clear maintained a PASI 50 response for a median duration of more than eight months.

In a combined treatment study with alefacept 15 mg once weekly and six weeks of UVB treatment tree times weekly, Ortonne et al demonstrated a PASI 50 response within 12 weeks in 22% to 90% of patients (at two different study sites) [192]. In the follow up period at week 24, 100% and 80% of these patients maintained their PASI 50 response (grade of evidence B).

Adverse drug reactions/safety

Adverse events are generally mild and do not lead to discontinuation of therapy in the vast majority of patients. Monitoring CD4+ T-cell counts is an important safety measure. Weekly

therapy should be interrupted if the CD4+ count falls below 250 cells/µL, and restarted once above this level.

Table 37: Overview of important side effects

Very frequent	None
Frequent	Mild headache; injection-site pain and inflammation; lowering of CD4+ count (seldom requires interruption of treatment)
Occasional	Infection, e.g. viral; flu-like syndrome; malignancies
Rare	none
Very rare	Asymptomatic transaminase elevation, fatty infiltration of the liver, hepatitis

Important contraindications/restrictions on use

Absolute contraindications

- HIV
- Pregnancy
- Systemic malignancy
- Hypersensitivity to alefacept or any of its components
- Active chronic Hepatitis B

Relative contraindications

– Active infection
– Hepatitis C
– CD4+ counts below 250 cells/µl
– Live vaccines

Drug interactions

Caution is advised in patients receiving concurrent immunosuppressive therapy (i.e. monitor CD4+ counts). Live-attenuated vaccines should not be administered during treatment with any of the biologic agents. Depending on their half-life, biologics should be discontinued four to eight weeks prior to an immunization and may be restarted two to three weeks later.

Instructions for use

Necessary measures
Due to the lack of long-term data, the guidelines development group feels that caution is advisable and monitoring during treatment should be performed. <u>Pre-treatment</u> • Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • History and clinical examination should focus on prior exposure to treatments, malignancies, and infections • Recommended measures include: – Check for skin cancer – Check for lymphadenopathy – Laboratory parameters (see Table 38, page 98) – Urine analysis – Pregnancy test • Contraception <u>During treatment</u> • Objective assessment of the disease (such as PASI/BSA/PGA, arthritis) • HRQoL (such as DLQI/Skindex-29 or -17) • History and clinical examination should focus on malignancies and risk factors for serious infections • Recommended measures include: – Check for skin cancer – Check for lymphadenopathy – Laboratory parameters (see Table 38, page 98) – Urine analysis • Contraception <u>Post-treatment</u> • After discontinuation of alefacept, patients should be followed up with medical

history and physical examination

- Physicians are encouraged to register their patients in a registry (if available)
- Assess CD4+ T cell count only if <250 cells/µl at the end of 12 weeks of treatment
- Reliable contraception until two months after treatment, if applicable. Because pregnancy is a contraindication for treatment, post-treatment contraception seems reasonable, although no data are available to support this recommendation

Overdose/measures in case of overdose

If the CD4+ T-cell count falls below 250 cells/µl, weekly injections should be interrupted. Treatment should be discontinued and the patient should be monitored for infections if the CD4+ T-cell count remains persistently below this level.

Table 38: Lab controls

	Period in weeks				
Parameter	Pre-treatment	4	8	12	Thereafter, every 3 months
Blood count	x	x	x	x	x
Liver enzymes	x	x			x
Serum creatinine	x	x			x
Urine sediment	x	x			x
Pregnancy test (urine)	x	x			x
ESR/CRP	x	x			x
HBV/HCV	x				
HIV	x				
CD4+ T cells	x	Every 2 weeks during treatment*			
Further specific testing may be required according to clinical signs, risk, and exposure.					

* to maintain count ≥ 250 cells/µL

Special considerations

- Slow initial response in all patients
- UVB therapy accelerates initial response

- CD4+ monitoring every two weeks

Safety aspects

There appears to be a very slight risk of an increased infection rate in clinical studies of alefacept. The most significant side effect is a reduction in the total lymphocyte count (CD4+ T cells) with 12 out of 156 (7.7%) patients in one phase III clinical study showing CD4+ T cell counts that were less than 300 cells/µl. In 11 of these patients, the counts subsequently returned to the normal range. This reduction in T-cell counts has been mirrored in subsequent clinical use, with the vast majority (>90%) of patients able to complete the 12-week course of treatment without interruption. There is no change in delayed-type hypersensitivity testing with alefacept, which is also considered a pregnancy category B drug.

Hepatitis/HIV

Although not mandatory, testing for HIV and hepatitis B and C infection is desirable, especially in patients who are at higher risk. Because of the risk of reactivation, chronic carriers of hepatitis B should not be treated with alefacept. Patients with hepatitis C should be appropriately evaluated and monitored during alefacept therapy.

Combination therapy

Alefacept can be combined with traditional systemic agents (methotrexate, ciclosporin, retinoids), as well as with phototherapy. Concomitant therapies can be safely recommended, including NB-UVB treatment, which may provide increased and more rapid efficacy.

Alefacept can be employed when transitioning patients from traditional systemic agents using an “overlap” approach and discontinuing prior systemic agents between weeks 4 and 12.

Table 39: Possibilities for therapeutic combination

	Recommendation	Comments
Methotrexate	+	In sequential use or low dose, up to end of 12-week course
Ciclosporin	+	In sequential use or low dose, up to end of 12-week course
Retinoids	+	10-25 mg daily
Fumaric acid esters	-	No clinical experience

Biologics	-	Cost and immunosuppression
Phototherapy	+	Narrowband or broadband UVB

Summary

A total of six studies fulfilled the criteria for inclusion in the guidelines; the overall level of evidence was classified as 1.

Alefacept had two pivotal phase III studies, in which a total of 1060 patients were treated with 12 weekly doses of alefacept vs. placebo. The primary endpoint was the PASI score at week 14 (i.e. two weeks after the last dose). This revealed a PASI 75 response in 33% of patients in the first study (intravenous alefacept), as well as a PASI 75 response in 21% of patients in the second study (intramuscular alefacept) [187, 190]. Of interest in this latter study was the continued improvement in the PASI score up to week 20 (i.e. eight weeks after the last dose). In the subsets of patients who achieved improvement with the first course, further improvement in the PASI score was noted after a 12-week interval.

The safety profile of alefacept has been excellent, both in phase II and III clinical studies, as well as in subsequent clinical use, with the most significant side effect being a reduction in the total lymphocyte count (CD4+ T cells) in 7.7% of the patients in one phase III clinical study (see Special considerations). This reduction in T-cell counts has been mirrored in subsequent clinical use, with the vast majority (>90%) of patients being able to complete the 12-week course of treatment without interruption.

An impressive aspect of this drug is the remission rates seen in a small percentage of patients, i.e. approximately 17% of patients in a recent article showing >6 months remission [193]. Thus, alefacept can be considered a true remittive drug in a small percentage of patients. However, at present it is impossible to predict which patients will achieve remission at this stage; ongoing and future pharmacogenomic studies will likely shed light on this subject.

Therapeutic recommendation

Alefacept is not suggested as a first choice among the biologics for induction therapy, although it may be efficacious in a small subgroup of patients. Selection criteria for these patients have not been established.

3.10 Efalizumab

Gisondi/Naldi

Introduction/general information

Efalizumab is a recombinant humanized monoclonal antibody directed against CD11a, the alpha subunit of leucocyte function-associated antigen-1 (LFA-1). The drug is approved in the European Union for the treatment of adult patients with moderate to severe chronic plaque psoriasis who have not responded to other systemic therapies, including ciclosporin, methotrexate, and PUVA, or for whom these are contraindicated or not tolerated. Efalizumab is supplied as a sterile, white, lyophilized powder in single-use glass vials for subcutaneous injection. Reconstitution of the single-use vial with 1.3 mL of the supplied sterile water for injection yields approximately 1.5 mL of solution to deliver 125 mg per 1.25 mL (100 mg/mL) of drug. The powder should be stored at 4°C until just prior to reconstitution [194].

Table 40: Tabular summary

Efalizumab	
Approval for psoriasis	September 2004 (EMEA)
Recommended controls	Full blood count, liver enzymes, ESR/CRP, creatinine, urine analysis, pregnancy test (urine), HBV/HCV, HIV (prior to therapy)
Recommended initial dose	0.7 mg/kg weekly (week 1)
Recommended maintenance dose	1 mg/kg weekly (from week 2 on)
Clinically significant response expected after	6-8 weeks
Response rate	PASI 75 in 30% of patients after 12 weeks
Absolute contraindications	Pregnancy/breastfeeding; severe chronic or acute infections, including active chronic hepatitis B; neoplasms; immune deficiencies; types of psoriasis other than chronic plaque psoriasis

Important side effects	Psoriasis exacerbation; arthralgia/arthritis; flu-like symptoms; immune-mediated haemolytic anaemia; immune thrombocytopenia
Important drug interaction	Not known
Special considerations	See applicable subchapter

Mechanism of Action

Efalizumab binds to CD11a, the α-subunit of LFA-1, which is expressed on all leucocytes, and decreases cell surface expression of CD11a. Efalizumab prevents the binding of LFA-1 to intercellular adhesion molecule-1 (ICAM-1), thereby inhibiting the adhesion of leucocytes to other cell types. Interaction between LFA-1 and ICAM-1 contributes to the initiation and maintenance of multiple immune processes, including activation of T lymphocytes, adhesion of T lymphocytes to endothelial cells, and migration of T lymphocytes to sites of inflammation of psoriatic skin. Lymphocyte activation and trafficking to skin play a role in the pathophysiology of chronic plaque psoriasis. In psoriatic skin, ICAM-1 cell surface expression is upregulated on endothelium and keratinocytes. CD11a is also expressed on the surface of B lymphocytes, monocytes, neutrophils, natural killer cells, and other leucocytes. Therefore, the potential exists for efalizumab to affect the activation, adhesion, migration, and numbers of cells other than T lymphocytes [195].

Dosing regimen

Efalizumab is administered by subcutaneous injection. The dose is dependent on body weight. The initial individual dose is 0.7 mg/kg, followed by a weekly maintenance dose of 1 mg/kg. After an initial treatment lasting 12 weeks, only those patients who have responded well to treatment (i.e. those reaching at least a PASI 50 response) should be further treated. Abrupt discontinuation of efalizumab may result in a recurrence or exacerbation of the psoriasis (rebound), as well as erythroderma and/or pustular psoriasis. The probability of a rebound is especially high in patients who have not responded early to efalizumab.

Efficacy

A total of nine studies, all of which investigated monotherapy with efalizumab, fulfilled the criteria for inclusion in the guidelines. Seven of the studies were assigned a grade of evidence of A2 [196-202], one a grade of evidence of B [203], and one a grade of evidence of C [204]. The overall level of evidence was classified as 1.

Optimal efficacy was observed with a weekly dose of 1 mg/kg. With this dose, seven studies demonstrated a PASI 75 response within 12 weeks in 22% to 38.9% of patients with moderate to severe psoriasis [196-200, 202, 204].

Using an intravenous dose of less than 1 mg/kg (0.1 or 0.3 mg/kg), Papp et al (grade of evidence A2) demonstrated a clearly poorer therapeutic effect [202]. A higher dose of 2 mg/kg weekly in the studies by Lebwohl et al (grade of evidence A2), Loenardi et al (grade of evidence A2), and Gottlieb et al (grade of evidence B) was equal to, or even less effective, than the 1 mg/kg dose [198, 199, 203]. The efficacy of efalizumab was confirmed for patients in whom other systemic therapies were unsuitable.

Approximately one third of the patients who had achieved at least a PASI 50 after twelve weeks attained a PASI 75 by 24 weeks in the studies by Lebwohl et al (grade of evidence A2) and Leonardi et al (grade of evidence A2) with continued treatment at doses of 1 mg/kg or 2 mg/kg. For patients with a PASI improvement lower than PASI 50, continued treatment did not result in any significant improvement [198, 199].

In their study, Dubertret et al included 526 high-need patients, defined as those for whom at least two systemic treatments were unsuitable due to lack of efficacy, intolerance, or contraindication. In this population, the treatment effect with a 1 mg/kg subcutaneous dose of efalizumab once weekly was similar to that seen in the ordinary study population, with a PASI 75 response within 12 weeks in 29.5% and 31.3% of patients [196].

In an open-label treatment study in which concomitant treatment with topical corticosteroids and UV therapy was permitted, a PASI 75 response was demonstrated in 40% of patients after three months. In this study, patients who had attained at least a PASI 50 response by week twelve showed a duration-dependent continued improvement when the treatment was continued. The therapeutic success with efalizumab can be further improved with continued treatment among patients in whom a response of at least PASI 50 has been achieved in the first twelve weeks. In patients with a PASI 75 within the first twelve weeks, the therapeutic success can be maintained with continued treatment. With a dose of 2 mg/kg for maintenance therapy following a PASI improvement of PASI 75, the administration of the drug once weekly was no more effective than every other week. In an open-label re-treatment study, Papp et al (grade of evidence C) showed that 56.9 % of patients who received at least twelve weeks of prior efalizumab therapy achieved a PASI 50 response after being re-treated with a 1 mg/kg weekly dose of efalizumab administered subcutaneously [204].

It should be noted that with interpreting the data for maintenance therapy one has to consider that the CD11a-saturation period for the dosage of 1 mg/kg is shorter than for 2 mg/kg, so the effective period is shorter [205].

In addition to the improvement of skin status mentioned above, patients reported a clear improvement in health-related quality of life (HRQoL) during therapy with efalizumab [206]. In the studies by Papp et al and Dubertret et al, an improvement of the sPGA, with a rating of minimal or clear, was demonstrated for 20.2% or 26.1% of patients in the efalizumab group compared to 4.2% or 3.4% of patients in the placebo group, respectively [13, 202].

Similar improvements were also described in other patient-reported data concerning the efficacy of treatment, including an improvement of itching [200, 202].

Adverse drug reaction/safety

The most common adverse drug reactions are flu-like injection reactions, including headache, chills, fever, nausea, and myalgia, occurring within two days following the first two injections. They occur in 30% of patients. When using a conditioning dose of 0.7 mg/kg for the first injection, the reaction is usually moderate in severity. Asymptomatic leukocytosis and lymphocytosis develop in 40% to 50% of patients, both of which are reversible after therapy. Efalizumab is an immunosuppressive agent and has the potential to increase the risk of infection (including severe infections) or to reactivate latent, chronic infections. Efalizumab should not be administered to patients with clinically important active infections. Caution should be taken when considering the use of efalizumab in patients with a chronic infection or a history of recurrent infections. If a patient develops a serious infection, efalizumab should be temporally discontinued. Efalizumab does not appear to increase the risk of reactivation of tuberculosis. No safety data are available in patients with chronic HCV or HBV infection or patients with latent tuberculosis. Lately there have been two reported cases of progressive multifocal leukoencephalopathy (PML) in patients on long-term treatment. These cases occurred in one 70-year old patient and one 73-year old patient who received raptiva for approximately four years. Concerning long-term treatment with efalizumab, estimated data point out that in the United States as of July 2008, approximately 700 patients have been exposed between 3 and 4 years, and at least 400 have been exposed for greater than 4 years [207]. Infrequent cases of severe, new onset arthralgia/arthritis events have been reported in clinical trials and post-marketing; to date, however, no estimates on their

incidence is available. In 0.3% of cases, thrombocytopenia has been reported. Very rarely, haemolytic anaemia and neuropathy (e.g. Guillan-Barré syndrome) have been reported.
The safety and efficacy of efalizumab in paediatric psoriatic patients have not been studied.

Limited evidence supports the notion that efalizumab is effective in elderly (age >65 years) as it is in the adult (18-65 years) psoriatic patients. Because the incidence of infections is generally higher in the elderly population, more caution should be taken in these patients.

Animal reproduction studies have not been conducted with efalizumab. It is also not known whether efalizumab can cause foetal harm when administered to a pregnant woman, or affect reproduction capacity. Because the effects of efalizumab on pregnant women and foetal development, including immune system development, are not known, women of child-bearing age should take adequate contraceptive measures if treated with efalizumab. Since immunoglobulins can pass through the placental barrier and are excreted with breast milk, pregnant women and breastfeeding mothers should not be treated with efalizumab [208].

Avoiding/treating side effects

Leucocytosis and lymphocytosis do not require treatment because they are a natural consequence of efalizumab's mechanism of action. Flu-like injection reactions can be managed with non-steroidal anti-inflammatory drugs. If acute infection is suspected, efalizumab should be temporarily discontinued until recovery from infection. A rapid rebound reaction after discontinuation of efalizumab or a psoriasis exacerbation during therapy (including pustular eruption and erythroderma) should be treated aggressively with immunosuppressive agents, including anti-TNF inhibitors [209]. In case of a rebound reaction, efalizumab can be restarted or the patient can be switched to another systemic treatment. If psoriasis exacerbation occurs during efalizumab treatment, methotrexate, ciclosporin, or phototherapy may be administered. If arthritis, thrombocytopenia, haemolytic anaemia, or neuropathy develop, efalizumab must be discontinued. Transient neutrophilic dermatosis generally responds to topical corticosteroids and does not require efalizumab discontinuation.

Table 41: Overview of important side effects

Very frequent	Leucocytosis, lymphocytosis, flu-like injection reactions (headache, chills, myalgia, fever, nausea, vomiting)
Frequent	
Occasional	Arthralgia/arthritis, psoriasis exacerbation during therapy

Rare	Thrombocytopenia, rebound after efalizumab discontinuation
Very rare	Haemolytic anaemia, neuropathy, progressive multifocal leukoencephalopathy

Important contraindications/restrictions on use

Absolute contraindications

- Malignancy (previous or current)
- Active infections (including tuberculosis)
- Active chronic Hepatitis B
- Immune deficiencies
- Types of psoriasis other than chronic plaque psoriasis (i.e. pustular, psoriatic arthritis, erythroderma)
- Pregnancy/breastfeeding

Relative contraindications

- Liver or renal failure
- Thrombocytopenia
- Haemolytic anaemia
- Hepatitis C
- Live vaccines

Drug interactions

No formal drug interaction studies have been conducted with efalizumab. Efalizumab should be used with caution in combination with other immunosuppressive drugs because of the potential for increased immunosuppression. Live-attenuated vaccines should not be administered during treatment with any of the biologic agents. Depending on their half-life, biologics should be discontinued four to eight weeks prior to an immunization and may be restarted two to three weeks later.

Instructions for use

Necessary measures
Due to the lack of long term-data, the guidelines development group feels that caution is

advisable and monitoring during treatment should be performed.

Pre-treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- History and clinical examination should focus on prior exposure to treatments; malignancies and infections; and thrombocytopenia and haemolytic anaemia
- Recommended measures include:
  - Check for skin cancer
  - Check for lymphadenopathy
  - Laboratory parameters (see Table 42, page 108)
  - Urine analysis
  - Pregnancy test
- Contraception

During treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Clinical examination should focus on malignancies and infections, as well as on thrombocytopenia and haemolytic anaemia
- Recommended measures include:
  - Check for skin cancer
  - Check for lymphadenopathy
  - Laboratory parameters (see Table 42, page 108)
  - Urine analysis
- Contraception

Post-treatment

- Patients who discontinue efalizumab should be subject to close follow-up. In cases of recurrence or exacerbation of the disease, initiation of another suitable psoriasis treatment is recommended. Patients should be informed about the possibility of rebound, which would make an immediate consultation necessary
- After discontinuation of efalizumab, patients should be followed up with medical

history and physical examination

- Physicians are encouraged to enrol their patients in a registry (if available)
- Reliable contraception until two months after treatment, if applicable. Because pregnancy is a contraindication for treatment, post-treatment contraception seems reasonable, although no data are available to support this recommendation

Overdose/measures in case of overdose

In dose-escalation studies with efalizumab, one patient who received an intravenous dose of 3 mg/kg suffered from hypertension, chills, and shivering requiring hospital treatment. Another patient suffered from serious emesis after receiving an intravenous dose of 10 mg/kg and needed to be admitted to hospital as well. Both pathologies disappeared without any after-effects. Doses up to 4 mg/kg weekly have been administered subcutaneously over a period of 10 weeks without any toxic effects [210]. There is no known antidote in case of overdose. Measures would include the discontinuation of therapy, as well as close monitoring of the patient and symptomatic treatment, if required.

Table 42: Lab controls

	Period in weeks				
Parameter	Pre-treatment	4	8	12	Thereafter, every 3 months
Full blood count	x	x	x	x	x
Liver enzymes	x	x			x
Serum creatinine	x	x			x
Urine sediment	x	x		x	x
Pregnancy test (urine)	x	x			x
ESR/ CRP	x	x			x
HBV/ HCV	x				
HIV	x				
Further specific testing may be required according to clinical signs, risk, and, exposure.					

Special considerations

TBC screening

Whether efalizumab increases the risk of reactivation of tuberculosis is not definitely known. TBC screening is recommended only in high-risk patients. If patients test positive, efalizumab can be administered and the patient closely monitored for TBC reactivation.

Infections

Although not mandatory, testing for HIV and hepatitis B and C infection is desirable, especially in patients who are at higher risk. Because of the risk of reactivation, chronic carriers of hepatitis B should not be treated with efalizumab. Patients with hepatitis C should be appropriately evaluated and monitored during therapy with efalizumab.

Drug-induced flare of psoriasis during therapy/rebound after discontinuation

Drug-induced flare of psoriasis during treatment with efalizumab has been documented. In case of psoriasis exacerbation during efalizumab treatment, methotrexate, ciclosporin, or phototherapy can be administered. The decision to discontinue efalizumab should be taken according the specific clinical setting. A rebound reaction after discontinuation of efalizumab, or an exacerbation of psoriasis during therapy (including pustular eruption and erythroderma), should be treated aggressively with immunosuppressive agents or anti-TNF-α inhibitors. In case of a rebound reaction, efalizumab can be restarted or the patient can be switched to another systemic treatment.

Combination therapy

Because efalizumab is a second-line therapy (i.e. to be used when conventional drugs are ineffective, not tolerated, or contraindicated), its combination with traditional drugs has never been formally investigated. Efalizumab should be used with caution in combination with other immunosuppressive drugs because of the potential for increasing immunosuppression. For combination, Methotrexate, ciclosporin, acitretin or phototherapy may be considered.

Table 43: Possibilities for therapeutic combination

	Recommendation	Comments
Methotrexate	+/-	Limited evidence. No formal studies [211]. Increased risk of immunosuppression
Ciclosporin	+/-	Authors' personal experience. No formal studies.

		Increased risk of immunosuppression
Retinoids	+/-	Case reports of successful combination exist [123]
Fumaric acid esters	-	No formal studies. Lack of experience
Biologics	-	No data. Increased risk of immunosuppression
Phototherapy	+/-	Authors' personal experience. No formal studies

Summary

A total of nine studies fulfilled the criteria for inclusion in the guidelines and showed that efalizumab is effective in the treatment of moderate to severe plaque psoriasis, with approximately 30% of treated patients achieving a PASI 75 response at week 12 (level of evidence 1).

Efalizumab is administered subcutaneously (initial dose 0.7 mg/kg, followed by a weekly maintenance dose of 1 mg/kg). Only responding patients (i.e. at least a PASI 50 response) should continue treatment after an initial 12-week course. Abrupt discontinuation of efalizumab may result in recurrence or exacerbation of psoriasis (rebound), as well as erythroderma and/or pustular psoriasis.

The most common adverse drug reactions are flu-like syndrome (30% of patients) and asymptomatic leucocytosis or lymphocytosis (40% to 50% of patients). Efalizumab should not be administered to patients with clinically important active infections. Caution should be taken in patients with a history of recurrent infections. Efalizumab is contraindicated in patients with a history of malignancy (previous or current).

Important note

Prior to the publication of these guidelines the European Medicines Agency (EMEA) had recommended the suspension of the marketing authorisation for efalizumab. After the occurrence of progressive multifocal leukoencephalopathy in patients taking the medicine the Committee for Medicinal Products for Human Use (CHMP) of the EMEA has concluded that, due to safety concerns, the benefits of efalizumab no longer outweigh its risks.

Therapeutic recommendation

Efalizumab is not suggested as a first choice among the biologics for induction therapy, although it may be efficacious in a subgroup of patients.

4 Phototherapy

Hönigsmann/Ferguson

Introduction

Various spectra of the UVB and UVA wavelengths are used for the treatment of psoriasis vulgaris. Photochemotherapy combines the initial topical or systemic administration of a photosensitizer with the subsequent exposure to light of the corresponding wavelength, generally UVA.

Originally, it was primarily a broad UVB spectrum with light waves of 280-320 nm that was used for psoriasis therapy; in the 1980s, phototherapy increasingly began to focus on the use of narrower spectra. The development of narrowband UVB fluorescence tubes with an emission peak at 311 nm made narrow-spectrum UVB therapy possible. Excimer lasers, which emit a monochromatic UVB light at 308 nm, have also been developed to treat psoriasis. Photochemotherapy consisting of the administration of photosensitizing psoralens with subsequent irradiation using UVA light (320-400 nm) has been employed since the 1970s. The different types of photochemotherapy include systemic (oral) PUVA treatment, as well as topical bath and cream PUVA.

Table 44: Tabular summary

Phototherapy	
Approval for psoriasis	More than 50 years of clinical experience, depending on the modality (Germany)
Recommended control parameters	Regular skin inspection, checking for UV erythema
Recommended initial dosage	Individual dose depending on skin type *Alternatives:* - UVB: 70% of minimum erythema dose (MED) - Oral PUVA: 75% of the minimum

	phototoxic dose (MPD) - Bath/cream PUVA: 20-30% of MPD
Recommended maintenance dose	Increase according to degree of erythema
Clinically significant response expected	After 1-2 weeks
Response rate	In >75% of the patients, PASI 75 after 4-6 weeks (level of evidence 2)
Important contraindications	Photodermatoses/photosensitive diseases, cutaneous malignancies Only PUVA: pregnancy or breastfeeding; treatment with ciclosporin
Important side effects	Erythema, itching, blistering, increased risk of cutaneous malignancies Only oral PUVA: nausea
Important drug interactions	Cave: Drugs causing phototoxicity or photoallergy
Special considerations	Combination with topical preparations is synergistic; PUVA should not be combined with ciclosporin

Mechanism of action

Phototherapy induces a variety of biological effects that probably contribute to its anti-psoriatic action. UV-induced immune suppression may play a major role. The anti-inflammatory effects of phototherapy include reduced mobility of antigen-presenting Langerhans' cells, inhibition of T-cell activation, and the induction of programmed cell death (apoptosis) in activated T cells [212]. Epidermal hyperproliferation is inhibited by the interaction of UV radiation with keratinocyte DNA, especially with regard to DNA synthesis. Anti-angiogenic effects have been detected that might also be therapeutically relevant [213].

Dosing regimen

The performance of phototherapy assumes extensive clinical experience on the part of the therapist. As a result of numerous variables, there are a multitude of therapeutic regimens. Table 45 through Table 50 shows sample regimens for various modalities:

Table 45: UVB phototherapy: initial doses [214]

Skin type	UVB broadband (mJ/cm^2)	UVB narrowband (mJ/cm^2)
I	20	200
II	30	300
III	50	500
IV	60	600

Table 46: UVB phototherapy: therapeutic regimen [214]

Step 1 Determination of the MED	Reading after 24h	
Step 2 Beginning of therapy	Initial dose	According to skin type or 70% of MED
Step 3 Treatment 3-5x weekly	No erythema	Increase by 30%
	Minimal erythema	Increase by 20%
	Persistent asymptomatic erythema	No increase
	Painful erythema	Break in therapy until symptoms fade
Step 4 Resume therapy	After fading of symptoms	Reduction of the last dose by 50%; further increase by 10%

Table 47: Localized UVB phototherapy (excimer laser or lamp): therapeutic regimen [215]

Step 1 Determination of the MED	Reading after 24h	
Step 2 Beginning of therapy	Initial dose	2x-4x of MED

Step 3 Treatment 2x weekly	Persistent asymptomatic erythema	Increase by 1x-2x MED
	Painful erythema	Break in therapy until symptoms fade
Step 4 Resume therapy	After fading of symptoms	Repeat with the last dose

Table 48: PUVA: common photosensitizers and their doses [214]

Modality	**Photosensitizer**	**Dose or concentration**
Oral PUVA	8-methoxypsoralen (8-MOP) 5-methoxypsoralen (5-MOP)	0.6 mg/kg 1.2 mg/kg
Bath PUVA	8-MOP	0.5-1.0 mg/l
CreamPUVA	8-MOP	0.0006-0.005% in Cream base with 30% H_2O (e.g. cold cream)

Table 49: PUVA: initial dosages [214]

Skin type	**Oral PUVA**		**Bath PUVA**
	(8-MOP) [J/cm2]	**(5-MOP) [J/cm2]**	**(1.0 mg/l 8-MOP) [J/cm2]**
I	0.3	0.4	0.2
II	0.5	1.0	0.3
III	0.8	1.5	0.4
IV	1.0	2.0	0.6

Table 50: PUVA: therapeutic regimen [214]

Step 1 Determination of the minimum phototoxic dose (MPD)	For oral PUVA: Reading after 72-96h For bath PUVA: Reading after 96-120h	
Step 2 Beginning of therapy	Initial dose	For oral PUVA:

		According to skin type or 75% of the MPD For bath PUVA: According to skin type or 30% of the MPD
Step 3 Treatment 2-4x weekly	No erythema, good response	Increase by 30% maximum 2x weekly
	Minimal erythema	No increase
	Persistent asymptomatic erythema	No increase
	Painful erythema	Break in therapy until symptoms fade
Step 4 Resume therapy	After symptoms fade	Reduction of the last dose by 50%; further increase by 10%

Efficacy

UVB (Broadband)

A total of six studies fulfilled the criteria for inclusion in the guidelines of which two were assigned a grade of evidence of A2 [216, 217] and four a grade of evidence of B [218-221].The A2 studies with conflicting results investigated the combination of UVB with topical therapy in which one arm each investigated UVB with placebo. Alttogether studies with treatment frequencies of two, three, five or seven exposures weekly were included for this modality. The percentage of patients with an improvement ≥ 75% was approximately 75%. The time needed to obtain this degree of improvement decreases from 12 to 4 weeks as the treatment frequency increases. A conflicting study showed that after eight weeks, three exposures weekly produced a 75% improvement in only 21% of patients [217]. Due to the conflicting results the overall level of evidence was classified as 3.

UVB (Narrowband)

A total of eight studies fulfilled the criteria for inclusion in the guidelines of which all were assigned a grade of evidence of B [60, 218, 222-227]. The level of evidence for narrowband UBV treatment was thus classified as 2. The treatment was performed either daily, twice, three times or four times weekly in the included studies. Clearance was achieved with two exposures weekly in 63% to 75% of cases within 20 weeks. With respect to the efficacy of four-times-weekly therapy, the results were inconsistent. One publication showed clearance

within seven weeks for all persons treated [224], and therefore superiority to twice weekly exposure, while the other showed 60% clearance over 10 weeks, which was comparable to the less frequent regimen [225]. Two further studies demonstrated a PASI 90 or PASI 100 result of 38% or 29% within 24 weeks or 10 weeks, respectively [60, 227]. For the first study, no treatment frequency was stated; the second study used a three times weekly exposure. In the only study with a daily exposure clearance was achieved in 86% after four weeks [218].

Home UVB phototherapy is a debated treatment. Although it is currently being prescribed for patients with psoriasis, literature on the subject is scarce. It appears a useful practical development considering that the most important reasons for prescribing home treatment are related to time and travel distance. In cases where appropriate training and support teams are available, home UVB phototherapy appears to be similar in efficacy to hospital therapy, as well as safe and cost-effective for patients [228]. To date, no randomized clinical studies of home UBV phototherapy have been conducted, and personal and non-evidence-based opinions on this form of treatment are widespread [229].

UVB 308 nm (excimer laser and excimer lamp)

Alltohether six studies fulfilled the guidelines inclusion criteria, four of which were assigned a grade of evidence of B [230-233] and two with a grade of evidence of C [234, 235]. Due to the different outcome parameters the overall level of evidence was classified 3. Because the excimer laser, for technical reasons, only allows for the exposure of individual psoriatic plaques, studies on the use of this technique usually treat target lesions. The application of localized delivery of laser light with a wavelength close to maximal efficiency in the treatment of psoriasis led to clinical investigations regarding the excimer laser for treatment of psoriasis [215]. Because non-involved skin is left unirradiated, an excimer laser represents the optimal method of delivery and dose for the treatment of psoriasis. Using multiples of the MED when treating psoriasis has been found to enhance the benefits and therapeutic response to laser light. The durability of clearing was also shown to be correlated with more aggressive treatment using 4x, 6x, and 8x multiples of the MED. As expected, using multiples of the MED produced very pronounced effects of marked erythema and blistering at the sites of delivery, although scarring at the sites was not observed. Another aspect of this approach to treatment is the reduction in the number of treatments needed to achieve the response [236]. Generally, 8 to 10 treatments can achieve a clearing of plaques. In one large [234] and several small randomized studies [215, 232, 233, 236], the treated areas demonstrated a good response after

multi-week therapy; the response ranged from partial remission to a complete healing of the skin lesions in all of the patients who completed the eight-week study [233]

Less complicated technology, using a high-intensity excimer lamp as the light source, has been developed for the treatment of psoriasis. These light sources emit 308 nm monochromatic light and are ideal for treating larger skin surfaces. The 308 nm excimer lamp has been shown to be as effective as the laser for the treatment of psoriasis [237].

PUVA

There are 20 studies available for oral PUVA therapy, two of which were assigned a grade of evidence of A2 [118, 238]. These were combination therapy studies with conflicting results in which one arm each investigated PUVA with placebo. From the other studies, 17 studies were assigned a grade of evidence of B [114, 239-253] and one a grade of evidence of C [254]. This results in a level of evidence of 2. In one study, 5-MOP in a dosage of 1.2 mg/kg served as photosensitizer; otherwise, 8-MOP in a dosage of 0.6 mg/kg was used or both dosages were compared. The treatment frequency was two to four exposures weekly, with the dose increase based on MPD or skin type. In the majority of studies, up to 90% of persons treated showed an improvement of ≥75%; this was true even with only two exposures weekly [248]. Two studies directly compared a dose increase according to skin type with MPD-based dose increase. The results were conflicting: in one study there was a minimum advantage for the MPD-based method [248], while in the other the skin-type-based method was clearly more effective [241] . In two comparative studies between 5-MOP and 8-MOP as a photosensitizer, 8-MOP was demonstrated to be superior [240, 242].

Four studies investigated the efficacy of bath PUVA. From these three studies investigated monotherapy, involving two [244], three [243], or four [255] exposures weekly, compared with oral PUVA therapy with the same treatment frequency. All three studies, which were assigned a grade of evidence of B, demonstrated an efficacy comparable to that of oral therapy or even better (level of evidence 2).

With regard to cream PUVA, one study compared it to oral PUVA [239] and another study compared it to UVB 311 nm [224]. Both studies were assigned a grade of evidence of B, resulting in a level of evidence of 2. In the first study, a 3x weekly cream PUVA therapy led to complete healing of the lesions (defined as ≥ 90%) in 88% of those treated. The efficacy was lower than with the oral PUVA comparison group with which four therapies weekly were performed. In the second study, with four treatments weekly, complete healing of lesions was

observed within five to seven weeks in all patients treated, which was the same therapeutic effect as that seen with 311 nm therapy.

Other modalities

One study comparing psoralen and UVB (PUVB) with classical oral PUVA therapy is available (grade of evidence B). It demonstrated that oral PUVA was more effective than PUVB, producing complete healing of lesions in 86% of patients, compared to 77% with PUVB 247. In a comparative study over eight weeks, 8-MOP bath and 311 nm UVB therapy produced complete healing in 38% of patients compared to 50% with saline bath and 311 nm UVB therapy 222. A combination of oral PUVA and UVB phototherapy led to a complete healing of the lesions in all patients after 17.0 ± 5.6 treatments and was therefore superior to the oral PUVA monotherapy in the same group (healing in 73% of the patients after about 20 exposures) 245. A similar study showed no difference in efficacy between the modalities. There was a complete healing of the lesions in all patients within nine treatments in both cases 249. All of the abovementioned studies in this section were assigned a grade of evidence of B, resulting in an overall level of evidence of 3 due to conflicting results. For further studies on phototherapy included by the systematic literature search [258-264] see the evidence tables.

Adverse drug reactions/safety

UVB (broadband, narrowband, 308 nm)

The available publications on UVB phototherapy contain little data on adverse effects. For all the UVB modalities, with the exception of excimer laser (308 nm), erythema is described as the most frequent adverse effect. The frequency of these are only mentioned in scattered cases and ranges from 33% for broadband UVB twice weekly [221] to 73% for narrowband UVB phototherapy [223]. Symptoms of a severe local UV erythema are frequently observed with the excimer laser. Typical adverse effects are, in particular, blisters, a burning sensation during therapy, and discolouration or hyperpigmentation [215, 233, 236]. Phototoxicity due to drugs does not pose a problem, because most photoactive drugs do not affect the UVB MED. If the MED corresponds to the patients' skin type, treatment can be performed without further precautions.

PUVA

Erythema, itching, and nausea are the most frequent adverse effects of oral PUVA. These adverse effects are not completely or consistently dealt with in the relevant studies. In comparable studies with three times weekly exposure, the frequency of erythema fluctuated

between 9% [256] and 80% [252]. The majority of the studies describe erythema in approximately 50% of the patients. In one publication [253], itching was the most frequent adverse effect, occurring in 83% of patients; otherwise it was reported in 25% [252] to 46% [250] of cases. Nausea was the third most commonly reported adverse effect, with a frequency of 35% [252, 253]. Dizziness is often mentioned, but data on its frequency (i.e. 60%) were presented in only one study. [240]. A correlation between the frequency of the adverse events and the frequency of treatment cannot be determined on the basis of the studies mentioned.

Studies on bath PUVA consistently report erythema and itching as the most frequent adverse effects [243, 244, 255]. A direct comparison of corresponding adverse effects with oral PUVA provided with the same frequency is possible in all of the studies, clearly demonstrating the superiority of bath PUVA. Erythema and itching occur much less often than with oral PUVA; nausea does not occur at all.

Erythema is also the most frequent adverse effect with cream PUVA [224, 239], but it is uncommon, occurring in approximately 5% of patients [224]. Beyond that, there are reports of blistering [224, 239].

Other modalities

Oral PUVA showed fewer side effects than PUVB in two studies, with lower rates of dizziness and nausea [247], as well as of erythema [223].

The combination of MOP bath and 311 nm phototherapy, as well as the combination of saline bath and 311 nm phototherapy, resulted in erythema with blisters in 10% of the patients treated with either modality [222].

Long-term safety (see [214])

As a result of the inclusion criteria for these guidelines, the discussion above does not contain any data on the long-term safety of the various types of phototherapy. The following comments reflect the recent Dutch guidelines.

Long-term UVB phototherapy results in actinic damage and premature aging of the skin. The potential carcinogenic effect of UVB phototherapy is controversial. Animal experiments have indeed shown a carcinogenic effect, but this appears less pronounced with narrowband therapy than with broadband UVB. The data available on human use are inconclusive. In contrast, the carcinogenic effect of oral PUVA therapy is well-established. The risk of developing squamous cell carcinoma and basal cell carcinoma increases as the number of

treatments increases. Although reports of an increased incidence of melanoma following long-term use exist, it is not possible to provide a definitive answer to the question regarding risk. In addition, poikiloderma, PUVA lentigines, and cataracts may develop with PUVA therapy.

Avoidance of adverse drug reactions

Clinically relevant adverse drug reactions are almost exclusively caused by UV erythema of various degrees as a result of an overdose. Isolated cases of death have been documented for oral PUVA. For this reason, close clinical monitoring of patients is required during phototherapy. One must look closely for erythema exceeding the desired clinical level. If there are clinical signs of UV erythema, therapy must be discontinued.

The kinetics of erythema formation are delayed with PUVA and not influenced by symptomatic measures such as corticosteroids. For that reason, special care must be taken with PUVA therapy. Many provide PUVA therapy four times weekly on Monday, Tuesday, Thursday, and Friday. This provides for breaks in the therapy that allow for early detection of erythema and thus timely interruption of treatment. Other adverse drug reactions of oral PUVA therapy can be reduced (carcinoma) or completely avoided (nausea) by applying the photosensitizers topically (bath or cream PUVA).

Since development of cutaneous malignancies correlates with the cumulative number of treatments, it should be monitored. This can be accomplished with a so-called UV passport, in which the total number of treatments and the doses are clearly documented. It is recommended that the cumulative lifetime UVA dose be limited to 1000 J/cm^2. Outcomes of pregnancies among women who received oral PUVA did not show any risk. However, it may be prudent for patients to avoid PUVA treatment during pregnancy whenever practical [257]. Breastfeeding women should not receive oral PUVA treatment, because psoralens are also excreted in the milk.

Table 51: Overview of important side effects

Very frequent	Erythema, itching, hyperpigmentation Only oral PUVA: nausea Only excimer laser: blistering
Frequent	–
Occasional	Blistering
Rare	Oral PUVA: squamous cell carcinoma, basal cell carcinoma
Very rare	–

Important contraindications/restrictions on use

Absolute contraindications

- Genetic defects causing increased photosensitivity or an increased risk of skin cancer, such as xeroderma pigmentosum, Cockayne syndrome, Bloom syndrome
- Lupus erythematosus
- Photosensitive dermatitis
- Present cutaneous malignancies

For PUVA:

- Treatment with ciclosporin [214]
- Pregnancy or breastfeeding

Relative contraindications

– Epilepsy
– Unavoidable use of photosensitizing drugs
– Skin type I
– Dysplastic melanocytic nevi
– History of skin cancer
– Poor compliance
– Physical or emotional inability to tolerate therapy (heart failure NYHA III-IV, claustrophobia)

In addition, the following relative contraindications should be observed in case of oral PUVA therapy:

– High cumulative number of treatments (more than 150-200 individual treatments)

– Previous therapy with arsenic or ionizing radiation
– Pronounced liver damage [214]

Drug interactions

Phototoxic or photoallergic drugs (Table 52) may lead to adverse effects when using PUVA because most photoactive drugs have an action spectrum in the UVA range. Therefore, prior to starting PUVA, the patient should be questioned about these drugs and they should be discontinued whenever possible.

Table 52: List of phototoxic or photoallergic drugs

Phototoxic drugs	**Photoallergic drugs**
Tetracyclines	Tiaprofenic acid
Phenothiazine	Promethazine
Griseofulvin	Chlorpromazine
Nalidixic acid	Hydrochlorothiazide
Furosemide	Quinine
Amiodarone	Suntan lotions (para-aminobenzoic acids, others)
Piroxicam	Disinfectants (hexachlorophene, others)
Tiaprofenic acid	
Dimethyltriazenoimidazole carboxamide	

Instructions for use

Dermatologists are generally well trained in administering phototherapy, as it is a required part of training programmes in most countries. When performing cream or bath PUVA therapy, topical photosensitizers must be applied appropriately and the interval between application and light exposure kept constant in order to optimize efficacy.

Necessary measures
<u>Pre-treatment</u>

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- History and clinical examination (complete skin examination) should focus on prior exposure, melanocytic nevi (especially if dysplastic), and cutaneous malignancies
- Additional UV exposure as a result of leisure-time activities should be considered
- Before starting oral PUVA therapy, the prescription of UVA protective sunglasses is required

<u>During treatment</u>

- Clinical examination
- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- The UV doses applied must be documented in precise physical units (J/cm^2 or mJ/cm^2)
- Regular monitoring of erythema must be performed for the purpose of dose increase.
- Medical records should document therapeutic response, unwanted side effects, and accompanying treatments
- Eye protection with UV-protective glasses during the treatment session is generally required; for oral PUVA, wearing UV-protective glasses is suggested for the 8 hours subsequent to medication intake
- If the areas chronically exposed to light (face, neck, backs of hands) and the genital region are free of lesions, they should be protected from exposure
- Sun avoidance or regular use of sunscreens is essential

<u>Post-treatment</u>

- Whenever a course of therapy is completed, the cumulative UV dose and the number of treatments should be recorded and the patient informed
- Particularly in the case of patients with a high number of treatments (200-250x), routine skin cancer examination should be performed for the patient's entire life

Overdose/measures in case of overdose

In the case of phototherapy, an acute overdose means UV erythema, while a chronic "overdose" leads to premature aging and an increased risk of cutaneous malignancies. If UV

Special considerations

Because the development of cutaneous malignancies correlates with the cumulative number of treatments, this number should be monitored. This can be accomplished with a so-called UV passport. It is recommended that the cumulative lifetime UVA dose be limited to 1000 J/cm^2. Furthermore, the patient should be informed about this possible long-term risk

Combination therapy

Many of the possible combination therapies for phototherapy and topical therapy have been assessed in controlled clinical studies. The combination of topical products with phototherapy generally did not result in a higher rate of adverse effects.

Table 53: Possibilities for therapeutic combination

	Recommendation	Comments
Methotrexate	+	No sufficient data available. Anecdotally used with success during the clearing phase
Ciclosporin	-	Contraindicated. Increased risk of squamous cell carcinoma reported for PUVA
Retinoids	++	Increased efficacy with reduced cumulative doses of UV [115, 117, 118]
Fumaric Acid Esters	+/-	No sufficient data available
Biologics	+/-	Evidence restricted to anecdotal reports

Summary

Of the 131 studies on monotherapy or combination therapy assessed, 56 studies on the different forms of phototherapy fulfilled the criteria for inclusion in the guidelines.

Approximately three quarters of all patients treated with phototherapy attained at least a PASI 75 response after four to six weeks, and clearance was frequently achieved (level of evidence 2 and 3). Phototherapy represents a safe and very effective treatment option for moderate to severe forms of psoriasis vulgaris. The onset of clinical effects occurs within two 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 use, the consequences of high, cumulative UV doses (such as 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 practicability of the therapy is limited by spatial, financial, human, and time constraints on the part of the physician, as well as by 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 for, and time required of, the patient must be considered.

Therapeutic recommendations

- Phototherapy is recommended as induction therapy for moderate to severe psoriasis vulgaris.
- Narrowband UVB is recommended as a first choice; PUVA is recommended in the event that UVB is not sufficiently effective.
- Because it is somewhat impractical and associated with long-term side effects as the cumulative number of treatments increase, phototherapy is not suitable for long-term treatment.
- The use of excimer lasers should be limited to the targeted treatment of individual psoriatic plaques.

5 Responsibilities

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6 Glossary

Appraisal of Guidelines Research & Evaluation Instrument	The Appraisal of Guidelines Research & Evaluation (AGREE) Instrument is an instrument for assessing the quality of clinical practice guidelines. The AGREE Instrument assesses both the quality of the reporting, and the quality of some aspects of recommendations. It provides an assessment of the predicted validity of a guideline, which is the likelihood that it will achieve its intended outcome. Therefore, the assessment includes judgements about the methods used for developing the guidelines, the content of the final recommendations, and the factors linked to their uptake.
Blinding	Hiding of the group assignment (therapy or control) from the patients and/or investigators and/or care personnel and/or evaluators who participate in a study.
body surface area	The body surface area (BSA) is a tool for estimating the involved body surface area of patients with psoriasis (in per cent). The BSA is easily evaluated either by the “rule of nines” method or by the number of patient’s hand areas affected (i.e. the area of one side of the patient’s flat closed hand is counted for 1% of his or her total BSA).
Dermatology Life Quality Index	The Dermatology Life Quality Index (DLQI) is a widely used dermatology-specific quality-of-life instrument. It consists of 10 questions related to the patient’s quality of life during the previous week on a four-point scale, indicating “not at all,” “a little,” “a lot,” and “very much.” The total DLQI score represents the sum of the scores for each question and ranges from 0 to 30. A high score reflects a worse quality of life.
Idiosyncratic reactions	Congenital or genetic, in some cases severe reactions to certain externally applied substances, even upon first contact. These reactions are not set off by a reaction of the immune system, but rather by dysfunction or malfunctioning enzymes or a lack

	of intact enzymes.
ITT	Intention-to-treat. Technique in which the patients are analyzed according to their originally assigned group, regardless of whether they received a therapy completely, partially, or not at all.
Minimal erythema dose	The minimal erythema dose (MED) is an objective value for the individual sensitivity towards a UV-wavelength used for phototherapy. The MED is defined as the least UV radiation dose of a certain wavelength causing a barely visible, sharply defined erythema. It is determined 24 hours after radiation. The MED assessment is conducted with the type of lamp that is designated for therapy and usually on non-light-exposed skin, and by gradually increasing the UV dose.
Minimal phototoxic dose	The minimal phototoxic dose (MPD) is an objective value for an individual's sensitivity towards photochemotherapy (PUVA). The MPD is the least UVA radiation dose causing a barely visible sharply defined erythema after intake of a photosensitizer. It is determined 72 hours after radiation. The MPD assessment is usually conducted on non-light-exposed skin.
Modified ITT	Modified intention-to-treat, also named quasi ITT, is a subset of the ITT population and allows the exclusion of some randomized subjects in a justified way.
Psoriasis Area and Severity Index	The Psoriasis Area and Severity Index (PASI) score is a clinical score for evaluating the severity of a patient's psoriasis. It describes the extent of the psoriasis, as well as the severity due to erythema. scaling, and thickness of the plaques. The maximum score is 72 points.
Psoriasis Disability Index	The Psoriasis Disability Index (PDI) is a validated self-administered psoriasis-specific questionnaire that consists of 10 questions including aspects of the patient's functional

	disability during the previous four weeks. Alternative versions of the PDI consist of 15 questions. The questions reflect daily activities, work, personal relationships, and treatment. Answers are recorded on a four-point scale, indicating grades from “not at all” to “very much.” The PDI correlates strongly with the DLQI.
Physician´s global assessment	The Physician´s Global Assessment (PGA) is a six-point score that summarizes the overall quality (erythema, scaling, and thickness) and extent (BSA) of plaques relative to the baseline assessment. A patient’s response is rated as worse, poor (0-24%), fair (25-49%), good (50-74%), excellent (75-99%), or cleared (100%).
Randomization	A method based on chance by which study participants are assigned to a treatment or control group. Randomization minimizes the differences among groups by equally distributing people among all the trial arms and therefore evenly distributing unknown, person-related disturbances.

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Appendices

Appendix 1: Literature Evaluation Form

Appendix 2: Summary Tables

Literature Evaluation Form (LEF)

No: …....

A. Inclusion/Exclusion of an Article:

This serves as a prescreening. If the article is not included, neither the quality nor the results will be assessed. (tick a grey box = exclusion of the article)

1. Author + Year: .....

2. Language: .....

3. Type of study: prospective study? yes ☐ no ☐

4. Number of patients ≥ 20? yes ☐ no ☐

5. Maintenance therapy study without interim results ≤ 16 weeks?
   yes ☐ no ☐ Induction and maintenance therapy study ☐

6. Exclusively adults (≥ 17 years)? yes ☐ no/n.d. ☐

7. Type of psoriasis: ≥75% of the study population with chronic plaque psoriasis (CPP) (psoriasis vulgaris)? yes ☐ no/n.d. ☐
   Exception: A study with less than 75% of the study population has CPP may be included if the efficacy data for chronic plaque-psoriasis (psoriasis vulgaris) is shown.

8. Type of therapy?
   monotherapy ☐ combination therapy ☐ distinct classification not possible ☐

9. Common dosage? yes ☐ no ☐
   E.g:
   Whole-body PUVA: maximum four times per week (only oral PUVA)
   Methotrexate: maximum 30mg per week
   Ciclosporine: maximum 5mg/kg/per day (Sandimmun®, Neoral®)

10. Objective outcome measure of efficacy described? yes ☐ no ☐
    For *Systemic- and Phototherapy:*
    Number of patients achieving ≥ *50%, 75% or 90% improvement described. 90% is equivalent to cleared or minimal disease or PASI 90.*

    For topical therapy not specified.

11. Exception:
    Article category: Review ☐ Safety study ☐ other☐
    Article should be quoted: yes ☐ no ☐

B. Quality of articles / Methods / will be partly published in table

1. Randomisation? Yes ☐ No ☐

2. Generation of randomisation sequence.
   Any information given? Yes ☐ No ☐ unsure ☐
   adequate ☐ non adequate ☐

3. Allocation concealment
   Adequate - eg third party or opaque sealed envelopes ☐ A
   Unclear - insufficient details provided ☐ B
   Inadequate - eg open list or day of week ☐ C
   Not used ☐ D

4. Blinding
   Participant/Patient Yes ☐ No ☐ unsure ☐
   Clinician Yes ☐ No ☐ unsure ☐
   Outcome assessor Yes ☐ No ☐ unsure ☐

5. Loss to follow-up
   Were all randomised participants included in the analysis in the groups to which they were randomised? (Intention to treat analysis?)
   Yes ☐ No ☐ unsure ☐

6. Clear definition of disease severity Yes ☐ No ☐ unsure ☐
   How defined: .....

7. Were groups comparable at baseline? Yes ☐ No ☐ unsure ☐
   Note any differences: .....

8. Interventions adequately described? Yes ☐ No ☐ unsure ☐

9. Previous treatment stopped Yes ☐ *No* ☐ unsure ☐

10. Study duration adequate? Yes ☐ No ☐ unsure ☐

11. Concomitant active treatment permitted? Yes ☐ No ☐ unsure ☐
    Details: .....

12. Assessment of compliance undertaken? Yes ☐ No ☐ unsure ☐
    Method: .....

13. Sponsorship
    Declared: Yes ☐ No ☐ unsure ☐
    Name: .....

C. Degree of Evidence

This article belongs to the following class:

A1 ☐ Meta-analyses which include at least one randomized clinical trial of A2 - level with consistent results of the different studies.

A2 ☐ Randomized, double blind clinical studies of good quality (e.g. sample size calculation, flow chart of patient inclusion, ITT - analysis, sufficient size)

B ☐ Randomized, clinical studies of less good quality or other comparable studies (not - randomized: cohort-, or case - control - studies)

C ☐ Non - comparable studies

D. Results / will be published in table

Methods / Results

1. Number of patients: .....

2. Maximal duration of treatment: .....

3. Intervention / Dosage scheme
   Arm 1: .....
   Arm 2: .....
   Arm 3: .....
   Arm 4: .....
   N.B. Please indicate the study design regarding the treatment groups and the dosage in each individual therapy arm.

4. Results / Definition of success of therapy/ Measure of effect

   Definition of success of the treatment: .....
   total remission ☐ partial remission ☐
   Point of time (should be close to 16 weeks): .....
   Arm 1: ….....
   Arm 2: .....
   Arm 3: .....
   Arm 4: .....

   Definition of success of the treatment: ….....
   total remission ☐ partial remission ☐
   Point of time: .....
   Arm 1: .....
   Arm 2: .....
   Arm 3: .....
   Arm 4: .....

5. If besides the total remission or partial remission another effect is described, please indicate the results (e.g. PASI, TSS) please give the results (e.g. average change in PASI-Score, inclusive 95% of confidence interval or standard deviation).
   Definition of alternative Score / Effect: .....
   Point of time: .....
   Arm 1: ….....
   Arm 2: .....
   Arm 3: .....
   Arm 4: .....

6. Remission/ Relapse described yes ☐ no ☐

   Definition of remission/ relapse …….....
   Duration of remission/ relapse:
   Arm 1: .....
   Arm 2: .....
   Arm 3: .....
   Arm 4: .....
   Duration of the follow up: ….....

7. ADRs specified

   What are the most important side effects (most frequent and most severe)?

Listing if not defined in detail: .....
.....
Arm 1: .....
.....
.....
Arm 2: .....
.....
.....
Arm 3: .....
.....
.....
Arm 4: .....
.....
.....

8. Losses to follow up

Arm 1	Arm 2	Arm 3	Arm 4
n =.....	n = ...	n = ...	n = ...
% = ……	% = ……	% = ……	% = ……

9. Dropouts caused by ADRs
   Did the patients predominantly drop out because of adverse effects?

Arm 1	Arm 2	Arm 3	Arm 4
yes ☐ no ☐	yes ☐ no ☐	yes ☐ no ☐	yes ☐ no ☐
n = ...	n = ...	n = ...	n = ...
% = ……	% = ……	% = ……	% = ……

Appendix 2

List of abbreviations

-	**no**
#	**link to bibliography**
+	**yes**
1x	**simple blind**
2x	**double blind**
3x	**triple blind**
AGREE	**Appraisal of Guidelines Research & Evaluation**
ADR	**adverse drug reaction**
BBUVB	**broad-band UVB**
BIW	**biweekly**
BSA	**body surface area**
BW	**body weight**
CSA	**ciclosporin**
d	**day**
EOW	**every other week**
F	**France**
GE	**grade of evidence**
IM	**intramuscular**
ITT	**intention-to-treat**
IV	**intravenous**
M	**month**
MED	**minimal erythema dose**
MOP	**methoxypsoralen**
MPD	**minimal phototoxic dose**
mR	**moderate remission**
MTX	**methotrexate**
n.a.	**not applicable**
NBUVB	**narrow-band UVB**
n.s.	**not stated**
PASI	**psoriasis area and severity index**
Pat.	**patient**
PGA	**psoriasis global assessment**
PO	**per os**

pR	**partial remission**
SC	**subcutaneous**
tbl.	**tablet**
TL01	**UVB 311 nm**
tR	**total remission**
US	**United States**
vs.	**versus**
W	**week(s)**
Y	**year**

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Methotrexate monotherapy																
Heydendael # 61	B	2003	88	16 W	MTX 15 mg/W after 4 W increase to max. 22.5 mg/W CSA 3mg/kg daily, after 4 W increase to max. 5 mg/kg daily	W 16	tR: 40% (17/43) pR: 60% (26/43) tR: 33% (14/42) pR: 71% (30/42)	n.a.	n.a.	tR: PASI 90 pR: PASI 75	n.a.	+	12 1	+	+	1x	n.s.
Nyfors # 63	C	1970	50	open	MTX 25 mg/W, then reduction of dose to 5 mg/W	n.s.	tR: 62% (31/50) pR: 20% (10/50) mR: 12% (6/50)	n.a.	n.a.	tR: improvement ≥ 95% pR: improvement 50 - 95% mR: improvement < 50%	n.a.	+	n.s.	n.a.	n.a.	n.a.	-
Weinstein # 56	C	1971	26	2-20M	MTX 7.5 - 22.5 mg/W (Weinstein regimen)	W 4 - M 3	tR: 77% (20/26) pR: 23% (6/26)	n.a.	n.a.	tR: improvement 75-100% pR: improvement 50-75%	n.a.	+	n.s.	n.a.	n.a.	n.a.	-
Methotrexate + other systemic therapy																
Asawanonda # 60	B	2006	24	24 W [1)]	MTX 15 mg/W + NBUVB Placebo + NBUVB	within 24 W	tR: 91% (10/11) tR: 38% (5/13)	n.a.	n.a.	tR: PASI 90	n.a.	+	1 4	-	+	2x	+
Morison [2)] # 62	C	1982	30	open	MTX 15mg/W + PUVA	until clear	tR: 93% (28/30) after mean 5.7 W	n.a.	n.a.	tR: BSA < 1 %	n.a.	+	0	n.a.	n.a.	n.a.	n.a.
Paul # 64	C	1982	26	16 W	MTX 15 mg/W (Weinstein regimen), from 4 th W on additional 3x/W UVB, from week 8 2x/W, from week 12 1x/W	W 7	tR: 100% (26/26)	n.a.	n.a.	tR: clearance	n.a.	+	0	n.a.	n.a.	n.a.	n.a.

1) **Plus 3 weeks MTX/Placebo beforehand**

2) **73,3% of patients with plaque psoriasis, other patients with erythrodermia or guttate type**

First author	Degree of Evidence	Year	Number of patients	Maximum duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Ciclosporin monotherapy																
Ellis # 82	A2	1991	85	16 W	Placebo CSA 3 mg/kg daily if necessary adaptation of dose after 8 W CSA 5 mg/kg daily if necessary adaptation of dose after 8 W	W 8	tR: 0% (0/25) tR: 36% (9/25) tR: 65% (13/20)	n.a.	n.a.	tR: PGA clear or almost clear	n.a. 2.78 [1.82 - 5.82] 1.54 [1.16 - 2.27]	+	4	+	+	2x	n.s.
Koo # 72	A2	1998	309	24 W	Neoral 2.5 mg/kg daily if necessary adaptation of dose after 5mg/kg daily Sandimmune 2.5 mg/kg daily if necessary adaptation of dose until 5 mg/kg daily	W 8	pR: 51.1% (78/152) pR: 38.2% (60/157)	n.a.	n.a.	pR: PASI 75	n.a.	+	59	-	+	2x	n.s.
Elder # 81	B	1995	37	12 W	Neoral 2x150 mg/d for 8 W then 4 W 2x150 mg/d Sandimmune Sandimmune 2x150 mg/d for 8 W then 4 W 2x150mg/d Neoral	W 12	tR: 88% tR: 82%	n.a.	n.a.	tR: PGA clear or almost clear	n.a.	+	6	-	+	2x	+
Engst # 83	B	1989	12	4 W	Placebo CSA 5 mg/kg daily	W 4	tR: 0% (0/6) pR: 16.7% (1/6) tR: 33.3% (2/6) pR: 50% (3/6)	n.a.	n.a.	tR: PASI 90 pR: PASI 75	n.a. tR: 3 [1.41 - ∞] pR: 3 [1.20 - ∞]	+	0	n.a.	+	2x	n.a.
Laburte # 89	B	1994	251	18M	CSA 2.5 mg/kg daily for 3 M afterwards increase to 5 mg CSA 5 mg/kg daily for 3 M. Try to reduce dose to 2.5 mg/kg, in case of relapse again 5 mg/kg	W 12	pR: 47.9% (57/119) pR: 88.6% (117/132)	n.a.	n.a.	pR: PASI 75	n.a.	+	88 [1)]	n.s.	+	-	n.s.
Meffert # 91	B	1997	128	22 W	Placebo CSA 1.25 mg/kg daily CSA 2.5 mg/kg daily	W 10	pR: ca. 5% [2)] pR: ca. 10% [2)] pR: 30% [2)]	n.a.	n.a.	pR: PASI 75	n.a.	+	23 [3)]	-	+	2x	n.s.
Thaci # 78	B	2002	122	24 W	CSA 100-300 mg/d CSA 1.25-5 mg/kg daily	W 12	pR: 89% (93/104)	n.a.	n.a.	pR: PASI 75	n.a.	+	18	n.s.	+	n.s.	+
Finzi # 84	C	1989	13	9 W	CSA 3 mg/kg daily, increase to 5mg/kg daily if no response	W 3	pR: 92.3% (12/13)	n.a.	n.a.	pR: PASI 75	n.a.	+	0	n.a.	n.a.	n.a.	n.a.
Higgins # 88	C	1989	17	12 W	CSA 5 mg/kg daily	W 12	tR: 70.6%	n.a.	n.a.	tR: BSA clearance	n.a.	+	0	n.a.	n.a.	n.a.	n.a.

First author	Degree of Evidence	Year	Number of patients	Maximum duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)		Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Ciclosporin vs. other therapy																	
Finzi # 85	B	1993	76	12 W	CSA 5 mg/kg daily	W 12	pR: 97.2% (35/36)	n.a.	n.a.	pR: PASI 75	n.a.	+	2	+	+	-	n.s.
					Etretinate 0.75 mg/kg daily for 2 W afterwards reduction to 0.5 mg/kg daily for 8 W [4)]		pR: 72.5% (29/40)						7	-			
Heydendael # 61	B	2003	88	16 W	MTX 15 mg/W, after 4 W increase to 22.5 mg/W	W 16	tR: 40% (17/43) pR: 60% (26/43)	n.a.	n.a.	tR: PASI 90 pR: PASI 75	n.a.	+	12	+	+	1x	n.s.
					CSA 3mg/kg daily, after 4 W increase to max. 5 mg/kg daily		tR: 33% (14/42) pR: 71% (30/42)						1				
Levell # 90	B	1995	60	16 W	CSA 5mg/kg daily	W 16	tR: 92.3% (24/26)	n.a.	n.a.	tR: PGA clear or almost clear	n.a.	+	10	-	+	-	-
					Dithranol 2-8% short contact + suberythemic UVB		tR: 83.3% (20/24)										
Mahrle # 80	B	1995	210	22 W	CSA 2.5 mg/kg daily, increase to 5 mg/kg daily if needed	W 10	pR: 78.8% tR: 19.7%	n.a.	n.a.	pR: PASI 60 tR: PASI 90	n.a.	+	42	-	+	-	n.s.
					Etretinate 0.5 mg/kg daily; if necessary increase to 0.75 mg/kg daily		pR: 31.9% tR: 4.4%										
Ciclosporin + systemic therapy																	
Reitamo # 93	A2 [4)]	2001	150	8 W	Sirolimus 0.5 mg/m² daily	W 8	pR: 18.8% (3/16)	n.a.	n.a.	pR: PASI 75 or PASI < 8	n.a.	+	56	-	+	2x	+
					Sirolimus 1.5 mg/m² daily		pR: 10.0% (2/20)										
					Sirolimus 3 mg/m² daily		pR: 15.0% (3/20)										
					Sirolimus 0.5 mg/m² daily + CSA 1.25 mg/kg daily		pR: 28.6% (6/21)										
					Sirolimus 1.5 mg/m² daily + CSA 1.25 mg/kg daily		pR: 20% (4/20)										
					Sirolimus 3 mg/m² daily+ CSA 1.25mg/kg daily		pR: 61.1% (11/18)										
					CSA 1.25 mg/kg daily		pR: 26.3% (5/19)										
					CSA 5 mg/kg daily		pR: 66.7% (10/15)										
Petzelbauer # 92	B	1990	40	until clear	CSA 5mg/kg daily + oral PUVA 4x/W	until clear	3.3 W	n.a.	n.a.	Time until clearance	-	+	3	-	-	-	-
					Etretinate 1mg/kg daily + oral PUVA 4x/W		3.7 W										
Franchi # 86	C	2004	6	9 W	CSA 200 mg/d for 3 W, then 100 mg/d for W 4-5, 2-3x/W UVB 311nm for 9 W	W 9	tR: 5/6 pR: 6/6 PR: 44,09	n.a.	n.a.	tR: 90 pR: 75 PR: mean PASI reduction	n.a.	-	0	n.a.	n.a.	n.a.	n.a.

First author	Degree of Evidence	Year	Number of patients	Maximum duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)		Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Ciclosporin + topical therapy																	
Grossman # 87	B [5)]	1994	69	6 W	CSA 2.0 mg/kg daily + placebo ointment	W 6	tR: 11.8% (4/34)	n.a.	n.a.	tR: PASI 90 or PGA "cleared"	n.a.	+	8	-	+	2x	n.s.
					CSA 2.0 mg/kg daily + calcipotriol 50µg/mg ointment 2x/d		tR: 50% (16/32)										

1) **Dropout data refers to dropouts between induction week (12 W) and phase II**
2) **Read out of graphic**
3) **In phase I: 8 dropouts, total: 23 dropouts**
4) **With regard to the evaluation of ciclosporin monotherapy GE B**
5) **With regard to the evaluation of ciclosporin monotherapy GE C**

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Retinoids monotherapy																
Kragballe # 105	A2	1989	168	12 W	Acitretin 40 mg/d (0.56 mg/kg/d) for 4 W, then may increase up to 80 mg/d	W 12	R: 11% (12/112) mI: 73% (82/112) PASI - 75.8%	n.a.	R: Remission mI: marked improvement PASI reduktion	n.a.	+	15	-	+	2x	-
					Etretinate 40 mg/d (0.56 mg/kg/d) for 4 W, then may increase up to 80 mg/d		R: 18% (7/39) mI: 62% (24/39) PASI - 70.8%					2				
Gupta # 116	B [2]	1989	38	8M	Placebo	W 8	pR: 11% (1/9) mR: 11% (1/9)	n.a.	pR: ≥ 75% mR: ≥ 50%	n.a.	+	5 [1]	-	+	2x	-
					Acitretin 10-25 mg/d		pR: 0% (0/8) mR: 0% (0/8)			n.a.						
					Acitretin 50-75 mg/d		pR: 25% (4/16) mR: 56% (9/16)			pR: 7.20 [2.30 - ∞] mR: 2.22 [1.30 - 7.51]						
Retinoids vs. other therapy																
Caca-Biljanowska # 114	B	2002	40	8 W	Oral PUVA 4x/W for 6 W, than 2x/W for 2 W	W 8	7/20	n.a.	Clearance	n.a.	+	0	n.a.	+	-	n.a.
					Acitretin 30mg/d initially, then according to package insert		10/20									
Retinoids + systemic therapy																
Saurat # 118	A2	1988	73	12 W	Placebo + oral PUVA after 2 W	W 12	tR: 80% (16/20)	n.a.	tR: ≥ 90%	n.a.	+	8	-	+	2x	-
					Etretinate 25mg/d + oral PUVA after 2 W		tR: 80% (16/20)									
					Acitretin 25mg/d +oral PUVA after 3 W		tR: 94% (17/18)									
Lauharanta # 117	B	1989	34	until clear	Bath PUVA 3x/W + acitretin 20-40 mg/d	until clear	57.2 d	n.a.	PASI 90	n.a.	+	0	n.a.	+	2x	n.a.
					Bath PUVA 3x/W + etretinate 20 mg-40 mg/d		56.9 d									
Carlin [3] # 115	C	2003	17	12 W	Acitretin 25mg/d+ solarium 5-7x/W (UVB-Anteil 5%, UVA 7-12%)	W 12	tR: 47% pR: 59%	n.a.	tR: PASI 90 pR: PASI 75	n.a.	+	3	-	n.a.	n.a.	+

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)		Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Retinoids + topical therapy																	
van de Kerkhof # 98	B [2)]	1998	135	12 W	Acitretin 20 mg/d, increased by 10 mg/W to maximum 70 mg/d + placebo	W 12	Clear: 41% (24/59)	n.a.	n.a.	Clearance/marked improvement (no definition)	n.a.	+	16	+	+	2x	+
					Acitretin 20 mg/d, increased by 10 mg/W to maximum 70 mg/d + calcipotriol ointment		Clear: 67% (51/76)						21	+			

1) **Phase I (8W), 5 dropouts; total (8M), 21 dropouts**

2) **Unclear definition of success of therapy lead to reduced GE**

3) **Additional retrospective part of the study, not included**

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Fumaric Acid Esters monotherapy																
Altmeyer # 125	A2	1994	100	16 W	Fumaderm initial until 2x1/d, then Fumaderm tbl. until 3x2/d	W 16	tR: 24% (12/50) [1] pR: 32% (16/50) [1] PR: PASI 21.5 →10.7	n.a.	n.a.	tR: RI ≥ 95% pR: RI = 70-95% PR: PASI reduction	tR: 5 [3.03 - 14.34] pR: 3.85 [2.47 - 8.70]	+	19	+	+	2x	+
					Placebo		tR: 4% (2/50) pR: 6% (3/50)						29	-			
Kolbach # 129	B	1992	196	24 M	Dimethylfumarate 60-240 mg/d	W 12	39% (41/104)	n.a.	n.a.	improvement ≥ 75% (no Score)	n.a.	+	25	-	-	-	n.s.
					Fumaderm initial 3x1/d, then Fumaderm until 2x2/d		53% (32/60)						7	+			
Nugteren-Huying # 132	B	1990	39	16 W	Fumaderm forte tbl. after scheme	W 16	tR: 50% (6/12) pR: 25% (3/12) BSA: 21% → 6%	n.a.	n.a.	tR: 90% BSA reduction pR: 70-90% BSA reduction	tR: 1.71 (1.16 - 3.29) pR: 12.00 (2.89 - ∞)	+	1	+	+	2x	-
					Octylfumaric acid 284 mg + Mg-+Zn-Salts		tR: 0/10. pR: 0/10 BSA unchanged				-		3				
					Placebo		tR: 0/12. pR: 1/12 BSA unchanged				n.a.		1	-			
Altmeyer # 124	C	1996	83	12M	Fumaderm initial until 3x1/d, then Fumaderm tbl. until 3x2/d	W 16	tR: 42% (35/83) pR: 29% (24/83) PR: PASI 26.04 → 5.43	n.a.	n.a.	tR: RI ≥ 95% pR: RI = 70-95% PR: PASI reduction	n.a.	+	33	-	n.a.	-	n.s.
Bayard [2] # 126	C	1987	13	3M	Fumaderm forte tbl., following regimen until max. 6 tbl/d	W 12	tR: 18% (2/11) pR: 27% (3/11)	n.a.	n.a.	tR: completely cured pR: no new areas, low activity	n.a.	+	2	+		n.a.	-
Carboni # 127	C	2004	40	24M	Fumaderm initial until 3x1/d, then Fumaderm tbl. until 3x1/d	W 12	tR: 21% (8/38) pR: 71% (27/38)	n.a.	n.a.	tR/ pR: no definition	n.a.	+	4	+	n.a.	n.a.	n.s.
Litjens # 130	C	2003	20	24M	Fumaderm tbl. folllowing regimen until 3x2/d	W 12	PASI 15 → 7 [1]	n.a.	n.a.	Significant PASI reduction	n.a.	+	8	+	n.a.	n.a.	n.s.
Mrowietz # 131	C	1998	101	16 W	Fumaderm initial until 3x1/d, then Fumaderm tbl. until 3x2/d	W 16	PASI 20.04 → 4.03 80% reduction	n.a.	n.a.	PASI reduction	n.a.	+	31	-	n.a.	n.a.	n.s.
Fumaric Acid Esters + topical therapy																
Gollnick # 128	A2	2002	134	13 W	Fumaderm initial 1x/d until Fumaderm 5x/d + 2x/d placebo ointment (n=66)	W 13	tR: 0% pR: 40% PR: PASI -51.9%	n.a.	n.a.	tR: clearance pR: marked improvement PR: PASI reduction	n.a.	+	20	+	+	2x	+
					Fumaderm same dose + 2x/d calcipotriol ointment (n=68)		tR: 10% pR: 65% PR: PASI -76.1%						14				

[1] **Read out of graphic**

[2] **Only evaluation study part Ia**

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Date of evaluation (maintenance)	Results (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominantely due to ADRs	Randomization	Blinding	ITT
Efalizumab																	
Dubertret # 196	A2	2006	793 (hnp: 526)[5]	12 W	Efalizumab 1 mg/kg 1x/W SC	W 12	pR: 31,4% (166/529) (hnp: 29,5%)[1] (101/342) mR: 53,7% (284/529) (hnp: 52,0%)[1] (178/342)	n.a.	n.a.	pR: PASI 75 mR: PASI 50	pR: 3.67 [3.14-4.43] hnp: 3.73 [3.11-4.66] mR: 2.55 [2.21-3.00] hnp: 2.66 [2.25-3.24]	+	53 (hnp:35)[1]	+	+	2x	+
					Placebo		pR: 4,2% (11/264) (hnp: 2,7%)[1] (5/184) mR: 14,4% (38/264) (hnp: 12,0%)[1] (22/184)				n.a.		17 (hnp:12)[1]	-			
Gordon # 197	A2	2003	556	12 W	Placebo	W 12	pR: 4% (8/187) mR: 14% (26/187)	n.a.	n.a.	pR: PASI 75 mR: PASI 50	n.a.	+	36	-	+	2x	+
					Efalizumab 1 mg/kg 1x/W SC		pR: 27% (98/369) mR: 59% (216/369)				pR: 4.49 [3.62-5.91]						
Lebwohl # 198	A2	2003	597	24 W	Placebo	W 12	tR: < 1% (1/122) pR: 5% (6/122)	n.a.	n.a.	tR: PASI 90 pR: PASI 75	n.a.	+	21 [2]	+ [2]	+	2x	+
					Efalizumab 1 mg/kg 1x/W SC		tR: 4% (10/232) pR: 22% (52/232)				tR: 28.65 [15.26-234.50] pR: 5.72 [4.15-9.18]		16 [2]				
					Efalizumab 2 mg/kg 1x/W SC		tR: 6% (15/243) pR: 28% (69/243)				tR: 18.68 [11.39-51.81] pR: 4.26 [3.30-6.01]		11 [2]				
Leonardi # 199	A2	2005	498	24 W	Placebo	W 12	tR: 1.2% (2/170) pR: 2.4% (4/170)	n.a.	n.a.	tR: PASI 90 pR: PASI 75	n.a.	+	53 [3]	-	+	2x	+
					Efalizumab 1 mg/kg 1x/W SC		tR: 12.3% (20/162) pR: 38.9% (63/162)				tR: 8.95 [6.07-17.09] pR: 2.74 [2.25-3.49]						
					Efalizumab 2 mg/kg 1x/W SC		tR: 4.8% (8/166) pR: 26.5% (44/166)				tR: 27.45 [13.73-26572.08] pR: 4.14 [3.20-5.86]						

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Date of evaluation (maintenance)	Results (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominantely due to ADRs	Randomization	Blinding	ITT
Menter # 200	A2	2005	556	24 W	Placebo	W 12	tR: 0.5% (1/187) pR: 4.2% (8/187) mR: 13.9% (26/187) MPR: nicht angegeben	n.a.	n.a.	tR: PASI 90 pR: PASI 75 mR: PASI 50 MPR: Mean PASI Reduction	n.a.	+	36 [4]	+	+	2x	+
					Efalizumab 1 mg/kg 1x/W SC		tR: 5% (19/369) pR: 26.6% (98/369) mR: 58.5% (216/369) MPR: 59.9%				tR: 21.67 [14.09-46.97] pR: 4.49 [3.62-5.91] mR: 2.24 [1.93-2.66]						
Papp # 201	A2	2001	145	8 W	Placebo	d 56	tR: 0% (0/48) pR: 2% (1/48)	n.a.	n.a.	tR: Total remission pR: PASI 75	n.a.	+	15	-	+	2x	-
					Efalizumab 0.1 mg/kg 1x/W IV		tR: 0% (0/22) pR: 5% (1/22)				pR: 40.62 [8.29-∞]						
					Efalizumab 0.3 mg/kg 1x/W IV		tR: 0% (0/75) pR: 25% (19/75)				pR: 4.30 [2.95-7.93]						
Papp # 202	A2	2006	686	12 W	Efalizumab 0,7 mg/kg (1x initial) + Efalizumab 1 mg/kg 1x/W SC (11W)	W 12	pR: 23,6% mR:52%	n.a.	n.a.	pR: PASI 75 mR: PASI 50	n.a.	+	29	-	+	3x	+
					Efalizumab 0,7 mg/kg (1x initial) + Placebo (11W)		pR: 3% mR: 14%	n.a.	n.a.				18	-			
Gottlieb # 203	B	2004	339	3 J	Efalizumab 2 mg/kg 1x/W + vaseline W 9 - 12	W 12	pR: 40%	n.a.	n.a.	pR: PASI 75	n.a.	+	31 [2]	-	+	-	+
					Efalizumab 2 mg/kg 1x/W + fluocinolone cream W 9-12		pR: 42%										
Papp # 204	C	2006	365	12 W (retreatment)[5]	Efalizumab 0,7 mg/kg (1x initial) + 1 mg (2 mg)[6]/kg/W SC (11W)	W 12	tR: 9,3% pR: 25,3% mR: 56,9%	n.a.	n.a.	tR: PASI 90 pR: PASI 75 mR: PASI 50	n.a.	+	19	-	-	-	-
Etanercept																	
Gottlieb # 148	A2	2003	112	24 W	Placebo	W 12	pR: 2% (1/55)	W 24	pR: 5%	pR: PASI 75	n.a.	+	8	-	+	2x	+
					Etanercept 25 mg 2x/W		pR: 30% (17/57)		pR: 56%		3.57 [2.48-6.40]						
Leonardi # 149	A2	2003	672	24 W	Placebo	W 12	pR: 4% (6/166)	W 24	n.a.	pR: PASI 75	n.a.	+	43	+	+	2x	-
					Etanercept 25 mg 1x/W		pR: 14% (23/160)		pR: 25%		9.29 [5.92-21.61]						
					Etanercept 25 mg 2x/W		pR: 34% (55/162)		pR: 44%		3.30 [2.62-4.44]						
					Etanercept 50 mg 2x/W		pR: 49% (81/164)		pR: 59%		2.18 [1.85-2.66]						

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Date of evaluation (maintenance)	Results (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominantely due to ADRs	Randomization	Blinding	ITT
Papp # 150	A2	2005	583	24 W	Etanercept 25 mg BIW SC	W 12	tR: 11% (22/196) pR: 34% (67/196) mR: 64% (125/196)	W 24	pR: 45%	tR: PASI 90 pR: PASI 75 mR: PASI 50	tR: 9.82 [6.72-18.04] pR: 3.22 [2.62-4.17] mR: 1.82 [1.59-2.12]	+	9	+	+	3x	+
					Etanercept 50 mg BIW SC W 0-12 Etanercept 25 mg BIW SC W 13-24		tR: 21% (41/194) pR: 49% (96/194) mR: 77% (149/194)		pR: 54%		tR: 4.98 [3.84-7.05] pR: 2.16 [1.86-2.57] mR: 1.47 [1.33-1.64]		9	-			
					Placebo		tR: 1% (2/193) pR: 3% (6/193) mR: 9% (17/193)		pR: 28%		n.a.		25				
Tyring # 151	A2[7)]	2006	618	96 W[7)]	Etanercept 50 mg 2xW SC	W 12	tR: 21% (65/311) pR: 47% (146/311) mR: 74% (230/311)	W 24	tR: 28% pR: 60% mR: 85%	tR: PASI 90 pR: PASI 75 mR: PASI 50	tR: 5.02 [4.07-6.55] pR: 2.38 [2.08-2.78] mR: 1.67 [1.51-1.86]	+	6	+	+	3x	.
					Placebo W 0-12 Etanercept 50 mg BIW (W 13-96)		tR: 1% (3/307) pR: 5% (15/307) mR: 14% (43/307)		tR: 17% pR: 48% mR: 76%		n.a.		17	-			
Cassano # 152	B	2006	108	12 W	Etanercept 50 mg (BIW)	W 12	pR: 54% mR: 74%	n.a	n.a	pR: PASI 75 mR: PASI 50	n.a.	+	3	-	+	1x	n.a.
					Etanercept 100 mg (once W)		pR: 50% mR: 78%						4				
Costanzo # 154	C	2005	44	24 W	Etanercept 2x25 mg/W SC	W 12	pR: 43% (19/44)	n.a.	n.a.	pR: PASI 75	n.a.	+	4	+	n.a.	n.a.	n.s.
Moore # 146	B	2007	2546	24 W	W 0-12: Etanercept 50 mg (BIW) W 13-24: Etanercept 50 mg (once W)	W 12	pR: 71.3%	W 24	pR: 71%	pR: PGA clear or almost clear	n.a.	+	42	-	+	-	+
					W 0-12: Etanercept 50 mg (BIW) from W 13 discontinuation and reinjection W 16 or W 20 [8)]		pR: 72%		pR: 59%				82				
Infliximab																	
Antoni [9)] # 167	A2	2005	200	22 W	Placebo	W 14	tR: 0% pR: 2% (2/87) mR: 9%	n.a.	n.a.	tR: PASI 90 pR: PASI 75 mR: PASI 50	n.a.	+	24	-	+	2x	n.s.
					Infliximab 5 mg/kg W 0/2/6		tR: 41% pR: 64% (53/83) mR: 82%				tR: 2.44 pR: 1.62 [1.38 - 1.97] mR: 1.37						

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Date of evaluation (maintenance)	Results (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominantely due to ADRs	Randomization	Blinding	ITT
Gottlieb # 169	A2	2004	249	6 W	Placebo	W 10	tR: 2% (1/51) pR: 5.9% (3/51) mR: 21.6% (11/51)	n.a.	n.a.	tR: PASI 90 pR: PASI 75 mR: PASI 50	n.a.	+	85	-	+	2x	n.s.
					Infliximab 3 mg/kg W 0/2/6		tR: 45.5% (45/99) pR: 72% (71/99) mR: 83.8% (83/99)				tR: 2.30 [1.85-3.03] pR: 1.52 [1.30-1.82] mR: 1.61 [1.32-2.05]						
					Infliximab 5 mg/kg W 0/2/6		tR: 57.6% (57/99) pR: 88% (87/99) mR: 97% (96/99)				tR: 1.80 [1.51-2.21] pR: 1.22 [1.10-1.37] mR: 1.33 [1.15-1.57]						
Reich # 170	A2	2005	378	46 W	Infliximab 5 mg/kg IV W 0/2/6 then every 8 W	W 10	tR: 57% pR: 80% mR: 91%	W 50	tR: 45% pR: 61% mR: 69%	tR: PASI 90 pR: PASI 75 mR: PASI 50	n.a.	+	31 (W 50)	+	+	3x	+
					Placebo W 0-24 Infliximab 5 mg/kg IV W 24-48		tR: 1% pR: 3% mR: 8%		tR: 50% pR: 77% mR: 90%				7 (W 24)	-			
													1 (W 50)	n.s.			
Chaudari # 168	B	2001	33	16 W	Placebo	W10	tR: 18% (2/11) PR: 20.3 → 17.5	n.a.	n.a.	tR: Mean PASI Reduction ≥ 75 % PR: PASI-Reduction	n.a.	+	3	-	+	2x	-
					Infliximab 5 mg/kg W 0/2/6		tR: 82% (9/11) PR: 22.1 → 3.8				tR: 1.57 [1.04-3.18]						
					Infliximab 10 mg/kg W 0/2/6		tR: 73% (8/11) PR: 26.6 → 5.9				tR: 1.83 [1.12-5.07]						
Schopf # 171	C	2002	8	6 W	Infliximab 5 mg/kg W 0/2/6	W 10	P-100: 37.5% (3/8) P-90: 25% (2/8) P-75: 25% (2/8) P-50: 12.5% (1/8)	n.a.	n.a.	PASI 100/90/75/50	n.a.	+	1	-	n.a.	n.a.	-
Smith # 172	C	2006	23	start: 2002 ongoing at end of trial (2005)	Infliximab 5mg/kg (W 0/2/6) 3-5 mg/kg (8-10 W intervalls) IV	W 10	pR: 77% mR: 95%	11 months	pR: 4/10 mR: 8/10	pR: PASI 75 mR. PASI 50	n.a.	+	7	+	-	-	n.s.

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Date of evaluation (maintenance)	Results (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominantely due to ADRs	Randomization	Blinding	ITT
Alefacept																	
Ellis # 187	A2	2001	229	12 W	0.025 mg/kg BW Alefacept IV 1x/W	W 14	pR: 21% (12/57) mR: 36% (21/57)	W 24	pR: 33% mR:47%	pR: PASI 75 mR: PASI 50	pR: 9.19 [4.17-∞] mR: 10.28 [3.76-∞]	+	6	-	+	3x	+
					0.075 mg/kg BW Alefacept IV 1x/W		pR: 33% (18/55) mR: 60% (33/55)		pR: 31% mR: 63%		pR: 4.4.3 [2.69-12.57] mR: 3.04 [2.00-6.38]		7				
					0.150 mg/kg BW Alefacept IV 1x/W		pR: 31% (18/58) mR: 56% (32/58)		pR: 19% mR: 42%		pR: 4.79 [2.85-14.97] mR: 3.56 [2.21-9.13]		9				
					Placebo		pR: 10% (6/59) mR: 27% (16/59)		pR: 11% mR: 32%		n.a.		10				
Krueger # 188	A2	2002	553	12 W	Alefacept 7.5 mg/W IV (W 1-12 and W 25-36)	W 14	pR: 14% (53/376) mR: 38% (143/376)	38[10]	pR:23% mR: 48%	pR: PASI 75 mR: PASI 50	pR: 9.68 [6.76-17.02] mR: 3.59 [2.91-4.70]	+	29	-	+	3x	+
					Alefacept 7.5 mg/W IV (W 1-12) Placebo (W 25-36)		see above, arm 1 and 2 together for W 1-12		pR 7% mR 25%				54				
					Placebo 1x/W IV (W 1-12)		pR: 4% (7/186) mR: 10% (19/186)	not continued	n.a.		n.a.		45				
Griebetz # 189	B	2005	20	16 W	Alefacept 15 mg 1x/W 12 W + 4 W Placebo	W 24	pR: 40% mR: 60%	n.a.	n.a.	pR: mean improvement of baseline PASI mR: PASI 50	n.a.	+	0	-	+	2x [11]	n.a.
					Alefacept 15 mg 1x/W 16 W		pR: 62% mR: 60%										
Ortonne # 190	B	2003	507	12 W	Alefacept 10 mg/W IM	W 14	pR: 12% (21/173)	within 24 W	pR: 28% mR: 53%	pR: PASI 75 mR: PASI 50	pR: 13.56 [7.57-64.88]	+	n.a.	n.a.	+	2x	n.a.
					Alefacept 15 mg/W IM		pR: 21% (35/166)		pR: 33% mR: 57%		pR: 6.13 [4.29-10.72]						
					Placebo		pR: 5% (8/168)		pR: 13% mR: 35%		n.a.						
Lowe # 191	C	2003	174	12 W	Alefacept 7,5 mg 1x/W IV[12]	within 14 W	pR: 39 % mR: 66%	n.a.	n.a.	pR: PASI 75 mR: PASI 50	n.a.	+	n.a.	-	-	-	n.a.
Alefacept + UVB																	
Ortonne # 192	B	2005	60	12 W	Alefacept 15 mg 1x/W IM	W 14	pR: 44% (F), 0% (US)	W 24	pR[14]: 88% (F) 0% (US)	pR: PASI 50	n.a.	+	2	-	+	-	n.s.
					Alefacept 15 mg 1x/W IM + UVB[13] (6W) 3x/W		pR: 90% (F), 22% (US)		pR[14]: 80% (F) 100% (US)				2	+			
					Alefacept 15 mg 1x/W IM + UVB[13] (12W) 3x/W		pR: 82% (F), 22% (US)		pR[14]: 90% (F) 75% (US)				1	-			
Adalimumab																	
Gordon # 139	A2	2006	147	60 W	Adalimumab 80 mg (W 0) + 40 mg EOW (from W 1) SC	W 12	pR: 53% tR: 11%	W 60	pR: 56% tR: 16%	pR: PASI 75 tR: PASI 100	n.a.	+	11	-	+	3x [15]	+
					Adalimumab 80 mg (W 0 + 1) + 40 mg weekly (from W 2) SC		pR: 80% tR: 26%		pR: 64% tR: 26%				17				
					Placebo (W 0-12) + Adalimumab 80mg (W 12) + 40mg EOW (W 13-60) SC		pR: 4% tR: 0%		pR: 45% tR: 19%				2 (W 12) 9 (W 60)				

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Date of evaluation (maintenance)	Results (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominantely due to ADRs	Randomization	Blinding	ITT
Menter # 140	A2	2007	1212	52 W[16)]	Adalimumab 80 mg (W 0) + 40 mg EOW SC (W 1 - W 15) Adalimumab 40 mg EOW (W 17 - W 33)[17)]	W 16	pR: 71% tR: 20%	W 24[18)]	pR: 70% tR: 22%	pR: PASI 75 tR: PASI 100	n.a.	+	61	-	+	2x	+
					Placebo (W 0) + EOW SC (W 1 - W 15) Adalimumab 40 mg EOW (W 17 - W 33)[17)]		pR: 7% tR: 0.8%						7	-			

1) **Hnp: high need population defined as unsuitability of at least two systemic treatments due to lack of efficacy, intolerance or contraindication**
2) **Refering to W 0-12**
3) **For patients in Efalizumab group**
4) **Course 1: 36, course 2: 50**
5) **Retreatment study after pretreatment with various dosages of Efalizumab in other studies**
6) **Dosage dependent on privious treatment with Efalizumab**
7) **W 0-12 double blind phase (Grade of Evidence A), from W 13 open label (Grade of Evidence B), long term results not shown**
8) **Interrupted group: responders (PGA of maximum 2 and improvement from baseline) discontinued and reinitiated at relapse (W16 or W20)**
9) **About 50% of patients with previous MTX therapy in both arms**
10) **Evaluation after 12 weeks follow-up (after first treatment) and 12 weeks retreatment**
11) **For placebo course**
12) **Retreatment of patients pretreated with different dosages of Alefacept in initial study 35 days ago or previously**
13) **France: Narrow Band UVB, US: Broad Band UVB**
14) **Percentage of the patients who had PASI 50 at week 14**
15) **From W 24 open label**
16) **Period C (W 33 - W 52) not shown in the table**
17) **Open label period for patients from either treatment arm of previous period who achieved PASI 75 at W 16, patients achieving less than PASI 75 at W 16 and who were randomized to adalimumab at W 0 entered a separate open label study arm with adalimumab 40 mg SC EOW**
18) **Pooling of efficacy outcomes from the main and the separate study arm of period B**

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UVB monotherapy																	
Coven # 218	B	1997	23	4 W	Narrow-band UVB daily Broad-band UVB daily	W 4	86% 73%	n.a.	n.a.	clearance	n.a.	+	1	+	-	-	n.s.
Leenutaphong # 225	B	2000	69	max. 40x	UVB 311nm 2x/W UVB 311nm 4x/W	40x	33/44 (75%) 15/25 (60%)	n.a.	n.a.	clearance after 40 treatments	n.a.	+	0	n.a.	-	-	-
UVB + systemic therapies (see Chapters on Retinoids, Biologics, Ciclosporin and Methotrexate)																	
Asawanonda # 60	B	2006	24	24 W [1]	MTX 15 mg/W + NBUVB Placebo + NBUVB	within 24 W	tR: 91% (10/11) tR: 38% (5/13)	n.a.	n.a.	tR: PASI 90	n.a.	+	1 4	-	+	2x	+
Orfanos # 219	B	1979	63	until clear	Etretinate + Broad-band UVB 4-5x/W Broad-band UVB 4-5x/W	until clear	22.9 x 26 x	n.a.	n.a.	number of treatments until nearly complete regression	n.a.	+	1	+	-	-	-
Ortonne # 192	B	2005	60	12 W	Alefacept 15 mg 1x/W IM Alefacept 15 mg 1x/W IM + UVB[2] (6 W) 3x/W Alefacept 15 mg 1x/W IM + UVB[2] (12 W) 3x/W	W 4	pR: 44% (F), 0% (US) pR: 90% (F), 22% (US) pR: 82% (F), 22% (US)	W 24	pR[3]: 88% (F) 0% (US) pR[3]: 80% (F) 100% (US) pR[3]: 90% (F) 75% (US)	pR: PASI 50	n.a.	+	2 2 1	- + -	+	-	n.s.
Carlin [4] # 115	C	2003	17	12 W	Acitretin 25 mg/d + solarium 5-7x/W (UVB fraction 5%, UVA 7-12%)	W 12	tR: 47% pR: 59%	n.a.	n.a.	tR: PASI 90 pR: PASI 75	n.a.	+	3	-	n.a.	n.a.	+
Franchi # 86	C	2004	6	9 W	CSA 200 mg/d for 3 W, then 100 mg at week 4-5, 2-3x/W UVB 311nm for 9 W	W 9	tR: 5/6 pR: 6/6 PR: 44.09	n.a.	n.a.	tR: 90 pR: 75 PR: mean PASI reduction	n.a.	-	0	n.a.	n.a.	n.a.	n.a.
Paul # 64	C	1982	26	16 W	MTX 15 mg/W (Weinstein regimen), from W 4 on additional UVB 3x/W	until clear	tR: 100% (26/26)	n.a.	n.a.	clearance	n.a.	+	0	n.a.	n.a.	n.a.	-
Levell # 90	B	1995	60	16 W	CSA 5 mg/kg BW/d Suberythemogenic UVB + dithranol 2-8% short contact	W 16	tR: 92.3% (24/26) tR: 83.3% (20/24)	n.a.	n.a.	tR: PGA clear or almost clear	n.a.	+	10	-	+	-	-
UVB vs. UVB + topical therapies																	
McBride # 258	B	2003	29	8 W	Dithranol short contact therapy 5x/W + Broad-band UVB 5x/W Dithranol short contact therapy 3x/W + Broad-band UVB 5x/W	W 8	11/25 10/25	n.a.	n.a.	PASI 75, halfside comparison	n.a.	+	4	-	+	1x	+
Dover # 216	A2	1989	53	until clear	UVB 3x/W + placebo cream 2x/d UVB 3x/W + fluocinonide cream 2x/d	variable	59% after an average of 90d 54% after an average of 85d	n.a.	n.a.	clearance	n.a.	-	18	-	+	2x	-
Petrozzi # 220	B	1983	26	max. 37x	Broad-band UVB 5x/W + fluocinolone 0.025/0.05% 2x/d Broad-band UVB 5x/W + placebo 2x/d	until clear	11/26 after 20x 09/26 after 23x	n.a.	n.a.	Halfside comparison, mean number of treatments until clearance	n.a.	+	0	n.a.	-	-	n.a.
Ring # 217	A2	2001	104	8 W	UVB 3x/W + calcitriol ointment 2x/d UVB 3x/W + placebo ointment 2x/d	W 8	45% 21%	n.a.	n.a.	Considerable improvement or clearance	n.a.	+	3	+	+	2x	+

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Ramsay # 221	B	2000	164	12 W	UVB 2x/W + Calcipotriol 2x/d	W 12	76,20%	n.a.	n.a.	PASI 80	n.a.	+	34 [5]	-	+	1x	+
					UVB 3x/W + vehicle 2x/d		73,40%										
Belsito # 259	B	1982	17	54d	Medium-wave UV 2x/d + coal tar 5% 2x/d	d 14	tR: 2/17 pR: 7/17	n.a.	n.a.	tR: ≥ 90% improvement pR: ≥ 75% improvement Halfside comparison	n.a.	-	0	n.a.	-	-	n.a.
					Medium-wave UV 2x/d + placebo 2x/d		tR: 2/17 pR: 8/17										
Diette # 245	B	1984	23	max. 33x	UVA + tar gel + UVB 3x/W [6]	until clear, max. 33x	tR: 10/13 pR: 12/13	n.a.	n.a.	tR: ≥ 90% improvement pR: ≥ 75% improvement Halfside comparison	n.a.	-	1	-	-	-	-
					UVB 3x/W + tar gel [6]		tR: 10/13 pR: 12/13										
					UVA 3x/W + coal tar 5% + UVA [7]		tR: 6/10 pR: 7/10 [8]										
					UVB 3x/W + coal tar 5% [7]		tR: 6/10 pR: 7/10 [8]										

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Date of evaluation (maintenance)	Results (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	Number of dropouts ADRs specified	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
LeVine # 260	B	1982	25	max. 27x	Halfside comparison: Ia:Coal tar 5% 5x/W vs. Ib: Fluocinonide + coal tar 5% 5x/W; on both sides UVB 7x/W Halfside comparison: IIa: Coal tar 5% + fluocinonide 5x/W vs. IIb: Fluocinonide 5x/W; on both sides UVB 7x/W Halfside comparison: IIIa: Vaseline + fluocinonide 5x/W vs. IIIb: fluocinonide 5x/W; on both sides UVB 7x/W Halfside comparison: IVa: Vaseline 5x/W vs. IVb: Fluocinonide + Vaseline 5x/W; on both sides UVB 7x/W Halfside comparison: Va: Coal tar 5% in Vaseline 5x/W vs. Vb: Fluocinonide + Vaseline 5x/W; on both sides UVB 7x/W	max. 27x	Ia 7/7 Pat. Ib+IIa 10/12 IIb+IIIb 9/9 IIIa+IVb+Va 10/11 IVa 5/5 Vb 2/2 (combined groups evaluated the same treatment)	n.a.	n.a.	tR: ≥ 95% BSA max. 27 treatments pR: ≥ 75% BSA after 5 treatments	n.a.	-	2	-	-	-	-

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Date of evaluation (maintenance)	Results (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	Number of dropouts ADRs specified	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Frost # 261	C 9)	1979	19	30x	Low dose suberythemogenic UV + tar gel 6)	after 10 to 30 treatments	Red. Sev. Sc: 81.5% (72.2 - 91.6%) 6 Pat.	n.a.	n.a.	clearance ≥ 95% improvement, Reduction of severity scores (Red. Sev.-Sc), halfside comparison	n.a.	-	3	-	+	-	-
					High dose erythemogenic UV + tar gel 6)		Red. Sev.-Sc.: 74.0% (60.6 - 86.6%) 6 Pat.										
					Suberythemogenic UV 7)		Red. Sev.-Sc.: 70.6% (70.4 -81.6%) 3 Pat.										
					Tar gel 7)		Red. Sev.-Sc.: 48.5% (43.0 - 59.1%) 3 Pat.										
					Suberythemogenic UV + tar gel 10)		Red. Sev. Sc. 70.1% (56.3 - 80.6%) 3 Pat.										
					Suberythemogenic UV+ placebo (tar gel vehicle) 10)		Red. Sev. Sc.: 53.8 (43.3 - 60.0%) 3 Pat.										
Koo # 262	B	2000	54	12 W	tazarotene 0.1% gel 14d, afterwards 3x/W broad-band UVB + tazarotene 0.1% gel 3x/W for 10 W	d 81	pR: 82%	n.a.	n.a.	pR: ≥ 75% Remission, intraindividual comparison of plaque	n.a.	+	14	-	+	1x	+
					Gel vehicle 14d, afterwards broad-band UVB 3x/W+ gel vehicle 3x/W for 10 W		pR: 68%										
					14d without treatment, afterwards broad-band UVB 3x/W for 10 W		pR: 50%										

1) **Plus 3 weeks MTX/Placebo beforehand**
2) **France: NBUVB, US: BBUVB**
3) **Percentage of the patients who had PASI 50 at week 14**
4) **Additional retrospective part of study which was not considered**
5) **29 during treatment phase, 5 at follow up**
6) **Halfside comparison of arm 1-2**
7) **Halfside comparison of arm 3-4**
8) **2 patients excluded because of erythrodermic psoriasis**
9) **Reduced GE because 3 non-responders excluded from ITT-analysis**
10) **Halfside comparison of arm 5-6**

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Date of evaluation (maintenance)	Results (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
PUVA vs. UVB																	
Arnold # 222	B	2001	40	8 W	MOP bath before Narrow-band UVB 3x/W	W 8	6/16 PR: 11.9+/-5.9 → 1.4 +/- 2.9	n.a.	n.a.	Complete clearance PR: PASI reduction	n.a.	+	7	-	+	-	n.s.
					Saline bath before Narrow-band UVB 3x/W		8/16 PR: 14.6+/-6.1 → 0.4 +/- 0.6										
Calzavara-Pinton # 263	B	1998	12	max. 20x	Bath PUVA 4x/W	until clear	tR: 3/12 PR: 9.13	n.a.	n.a.	tR: PASI 95 PR: mean PASI reduction, Halfside comparison	n.a.	+	0	n.a.	+	-	n.a.
					Bath PUVA+UVB 311nm 4x/W		tR: 11/12 PR: 12.71										
Gordon # 223	B	1999	100	20 W	PUVA 2x/W after MPD	until clear	tR: 84% (41/49)	n.a.	n.a.	tR: clearance above knees	n.a.	+	7	-	+	1x	+
					UVB 311 nm 2x/W after MPD		tR: 63% (32/51)										
Grundmann-Kollmann # 224	B	2004	30	3-7 W	UVB 311nm 4x/W	until clear	5-7 W 21 +/-3 treatments	n.a.	n.a.	Time until clearance, mean number of treatments until clearane	n.a.	+	0	n.a.	+	-	+
					Cream PUVA 4x/W		5-7 W 24 +/- 5 treatments										
					Cream PUVA + UVB 4x/W		3-4 W 14 +/- 2 treatments										
Markham # 226	B	2003	54	until clear	UVB 311nm 3x/W	until clear	25.5d	n.a.	n.a.	Time until clearance	n.a.	+	9	-	+	-	-
					PUVA (8-MOP 0.6 mg/kg/BW) 2x/W		19d										
Parrish [1] # 251	B	1974	16	until clear	Conventional UVA 275 - 380 nm	W 4	16/16	n.a.	n.a.	clearance/ halfside comparison	n.a.	+	0	n.a.	+	-	n.a.
					Oral PUVA 310 - 390 nm		16/16										
Snellman # 227	B	2004	18	10 W or clear	Bath PUVA: 3x/W	W10 or clear	tR: 1/17	n.a.	n.a.	tR: ≥ 100% Halfside comparison	n.a.	+	2	+	+	1x	+
					Narrow-band UVB 3x/W with 50% MED		tR: 5/17										
Psychosocial therapy + UVB / PUVA																	
Kabat-Zinn # 51	B	1998	37	125 d	UVB 3x/W	until clear	4/10 after 121d	n.a.	n.a.	Time until clearance (PASI 95) in 50% of patients	n.a.	-	14	-	+	1x	+
					UVB + meditation		5/11 after 84d										
					PUVA 3x/W		5/8 after 112d										
					PUVA + meditation		5/8 after 78d										

[1] **not all arms listed**

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Oral PUVA / PUVB / PUVA + UVB																
Berg # 240	B	1994	38	9 W	5-MOP 1.2 mg/kg 2x/W PUVA 8-MOP 0.6 mg/kg 2x/W PUVA	W 9	tR: 5/14 pR: 7/14 tR: 11/15 pR: 13/15	n.a.	n.a.	tR: PASI 90 pR: PASI 75	n.a.	+	9	+	+	2x	-
Buckley # 241	B	1995	83	until clear	Oral PUVA based on skin type 3x/W Oral PUVA based on MPD 2x/W	until clear	66.5 J/cm² 78.5 J/cm²	n.a.	n.a.	kD: cumulative dose until clearance	n.a.	+	8	+	+	n.s.	-
Calzavara-Pinton # 242	B	1992	25	until clear	5 MOP 1.2 mg/kg 8 MOP 0.6 mg/kg	until clear	22.1 treatments. 179.1 J/cm² 22.6 treatments. 117.7 J/cm²	n.a.	n.a.	Mean number of treatments until clearance, total UVA dose	n.a.	+	0	n.a.	n.s.	-	n.a.
Calzavara-Pinton # 255	B	1994	22 [1)]	until clear	Bath PUVA 4x/W Oral PUVA 4x/W	until clear	tR: 14/22 15.2 treatments tR: 12/22 20.6 treatments	n.a.	n.a.	tR: ≥ 100% mean number of treatments	n.a.	+	0	n.a.	-	-	n.a.
Diette [2)] # 264	B	1984	31	4 W	Oral PUVA 2x/W Oral PUVA + UVB 2x/W	until clear	8/11 (19.7 +/- 7.7 treatments) 11/11 (17.8 +/- 5.6 treatments)	n.a.	n.a.	Clearance	n.a.	-	0	n.a.	-	-	n.a.
Khurshid # 247	B	2000	44	max. 17 W	Methoxypsoralen 0.6 mg/kg followed by PUVB based on skin type Methoxypsoralen 0.6 mg/kg followed by PUVA based on skin type	W 7 or clear	17/22 after 5.2 d. kD: 25.2 J/ cm2 19/22 after 6 d. kD: 72.5 J/ cm2	n.a.	n.a.	Clearance after mean x days, kD: cumulative dose	n.a.	+	0	n.a.	+	-	n.a.
Kirby # 248	B	1999	85	21-105 d	PUVA 2x/W based on MPD PUVA 2x/W based on skin type	until clear	tR: 67.5%. MPD-PUVA: 44.5 d (21-97 d) tR: 95% skin type-PUVA: 66 d (33-105 d)	n.a.	n.a.	Mean days until tR: ≥100 %	n.a.	+	5	-	+	-	-

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)		Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Park # 249	B	1988	19 [1]	until clear	Oral PUVA 2-3x/W	until clear	19/19 (9.5 +/- 4.3 treatments)	n.a.	n.a.	Time until clearance ≥ 95%, halfside comparison	n.a.	-	0	n.a.	-	-	n.a.
					Oral PUVA 2-3x/W + UVB		19/19 (8.5 +/- 3.5 treatments)										
Henseler # 254	C	1981	3175	20x	Oral PUVA 4x/W	after 20x	tR: 65.2% pR: 88.8%	n.a.	n.a.	tR: ≥ 95% pR:≥ 75% after 20 days of treatment	n.a.	+	231	-	n.a.	n.a.	+
Oral PUVA vs. topical PUVA																	
Barth # 239	B	1978	148	15 W	Topical PUVA 3x/W	until clear	tR: 88.3%	n.a.	n.a.	tR: ≥ 90% after mean 18 exposures (irradiations)	n.a.	+	n.s.	n.s.	n.s.	-	n.a.
					Oral PUVA 4x/W		tR: 94%										
Collins # 243	B	1992	44	7 W	Bath PUVA 3x/W	20x	14/22 kD: 14.5 J/cm2	n.a.	n.a.	Clearance, cumulative UVA dose	n.a.	+	4	+	+	1x	-
					Oral PUVA 3x/W		14/22 kD: 60.1 J/cm2										
Cooper # 244	B	2000	34	until clear	Oral PUVA 0.6 mg Methoxypsoralen/kg 2x/W	20x or clear	14/17 kD: 84.7 J/cm2	n.a.	n.a.	Clearance kD: cumulative dose	n.a.	+	0	n.a.	+	-	n.a.
					Bath PUVA 2x/W		17/17 kD: 34.7 J/cm2										
PUVA + systemic therapy (see chapters on Ciclosporin, Retinoids)																	
Saurat # 118	A2	1988	73	12 W	Placebo + PUVA after 2 W	W 12	tR: 80% (16/20)	n.a.	n.a.	tR:≥ 90%	n.a.	+	8	-	+	2x	-
					Etretinate 25 mg+ PUVA after 2 W [3]		tR: 80% (16/20)										
					Acitretin 25 mg+ PUVA after 3 W		tR: 94% (17/18)										
Lauharanta # 117	B	1989	34	until clear	Bath PUVA 3x/W + acitretin 20 mg/d - 40 mg/d	until clear	57.2 d	n.a.	n.a.	PASI 90	n.a.	+	0	n.a.	+	2x	n.a.
					Bath PUVA 3x/W + etretinate 20 mg/d - 40 mg/d		56.9 d										
Parker # 250	B	1984	28	max. 10 W	Oral PUVA 3x/W + placebo	until clear	9/13 (49.9 days mean)	n.a.	n.a.	Clearance = less than 2% body surface affected	n.a.	+	2	-	+	2x	-
					Oral PUVA 3x/W + etretinate 0.75 mg/kg daily [3]		14/15 (40.3 days mean)										

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)		Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Petzelbauer # 92	B	1990	40	until clear	CSA 5 mg/kg daily + oral PUVA 4x/W	until clear	3.3 W	n.a.	n.a.	Mean weeks until clearance	n.a.	+	3	-	-	-	-
					Etretinate 1 mg/kg daily + oral PUVA 4x/W [3]		3.7 W										
Morison [3] # 62	C	1982	30	open	MTX 15 mg/W + PUVA	W 5.7	tR: 93% (28/30) after an average of 5.7 W	n.a.	n.a.	tR: BSA < 1 %	-	+	n.s.	n.a.	-	n.s.	-
PUVA + topical therapy																	
Frappaz # 256	A2	1993	107	12 W	PUVA (0.6 mg/kg) + UVA 3x/W + 2x/d placebo ointment	W 12	29/46 after 34 d	n.a.	n.a.	PASI 75	n.a.	+	15	-	+	2x	-
					PUVA (0.6 mg/kg) + UVA 3x/W + 2x/d Calcipotriol (50µg/g)		40/46 after 22 d										
Torras # 238	A2	2004	120	10 W	Calcipotriol 2x/d + PUVA 3x/W	W 10	pR: 87.9% tR: 69%	n.a.	n.a.	tR: PASI 90 pR: PASI 75	n.a.	+	11	-	+	2x	+
					Vehicle + PUVA 3x/W		pR: 47.3% tR: 36.4%										
Hanke # 246	B	1979	12 [1]	30x	Oral PUVA 2-3x/W + placebo ointment	until clear	tR: 12/12. 20.25 treatments. kD: 133.71 J/cm²	n.a.	n.a.	Halfside comparison, mean number of treatments until tR, kD: cumulative dose until clearance	n.a.	-	0	n.a.	+	2x	n.a.
					Oral PUVA 2-3x/W + betamethasone dipriopionate		tR: 12/12. 13.58 treatments. kD: 69.96 J/cm²										
PUVA vs. other therapy																	
Caca-Biljanowska # 114	B	2002	40	8 W	Oral PUVA 4x/W for 6 W, afterwards 2x/W for 2 W	W 8	7/20	n.a.	n.a.	Clearance	n.a.	+	0	n.a.	+	-	n.a.
					Acitretin 30 mg daily initially, then following package insert		10/20										
Rogers [4] # 252	B	1979	224	until clear	Oral PUVA 3x/W	until clear	Mean 34.4 +/- 1.8 d: 91% (103/113)	n.a.	n.a.	Mean number of days until clearance	n.a.	+	4	n.s.	+	-	n.s.
					Ingram regimen (coal tar bath, UV light with unclear bandwidth, dithranol)		Mean 20.4 +/- 0.9 d: 82% (91/111)										

First author	Degree of Evidence	Year	Number of patients	Maximal duration of treatment	Dosage	Date of evaluation	Results	Results (maintenance) Date of evaluation (maintenance)	NNT vs. placebo	Definition of success of therapy Measure of effect	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Vella Briffa [4] # 253	B	1978	224	until clear	Oral PUVA 3x/W Ingram regimen (coal tar bath, UV light with unclear bandwidth, dithranol)	until clear	Mean 34.4 +/- 1.8 d: 91.2% (103/113) Mean 20.4 +/- 0.9 d: 82% (91/111)	n.a.	n.a.	Mean number of days until clearance	n.a.	+	33 [5]	n.s.	+	-	-

1) **halfside comparison**
2) **not all arms listed**
3) **the study included 73.3% patients with plaque-type psoriasis; the rest had psoriatic erythroderma or guttate psoriasis**
4) **same collective, duplicate publication**
5) **dropouts after randomization but before beginning the therapy**

First author	Degree of Evidence	Year	Number of patients	Maximual duration of treatment	Dosage	Date of evaluation	Results	Date of evaluation (maintenance)	Results (maintenance)	Definition of success of therapy Measure of effect	NNT vs. placebo	ADRs specified	Number of dropouts	Dropouts predominately due to ADRs	Randomization	Blinding	ITT
Laser monotherapy																	
Hacker # 230	B	1992	20	8 W	0.0 J/cm2 5.0 J/cm2 7.0 J/cm2	W 8	No success	n.a.	n.a.	Mean decrease in severity scores for erythema, scaling, thickness of plaque: "clinical positive effect" (not defined); 4 quadrant comparison	n.a.	-	1	-	-	1x	n.s.
					9.0 J/cm2		Erythema: 3.84 → 2.09 scaling: 4.00 → 1.55 PD: 4.11→1.45 57% (11/19) "clinical positive effect"				1.73 [1.25 - 2.80]						
Katugampola # 231	B	1995	8	6 W	No therapy	W 16	tR: 0 pR: 0	n.a.	n.a.	tR: 100% improvement of Plaque Severity Scores pR: > 50% improvement of PSS; comparion of 2 main lesions	n.a.	+	1	n.s.	-	n.s.	-
					8.5 J/cm². 3x/W in week 2/4/6		tR: 1/7 pR: 5/7				tR: 7.00 [2.49 - ∞] pR: 1.40 [1 - 2.63]						
Taibjee # 232	B	2005	22	12 W	Excimer laser (0.6 - 2.1 J cm^{-2}, 2x/W)	W 12	pR: 4.7 tR: 9 (41%)	M12	tR: 4/7[2]	pR: improvement of mean PASI tR: clearance	n.a.	+	7	-	-	-	n.s.
					Pulse dye laser (10 -12 J cm^{-2}, every 4 W)[1]		pR: 2.7 tR: 6 (27%)		tR: 4/6[3]								
					Salicylic acid 6%		pR: 1.8 tR: 2	n.a.	n.a.								
					Untreated control		pR: 1.2 tR: 1										
Trehan # 233	B	2002	20	8 W	3x/W for 8 W dose 100-350 mJ/cm2 dose after MED	W 8	tR: 100% (15/15)	n.a.	n.a.	tR of main lesions: PASI 95 comparison of plaques: 6 verum Plaques/Patient, 1 placebo Plaque/Patient	tR: 1.00 [1.00 - 1.00]	+	5	-	-	n.s.	-
					No therapy		tR: 0% (0/15)				n.a.						
Feldman # 234	C	2002	124	5 W 10x	Excimer laser 308nm, (100-350 mJ/cm^2 dependent on MED)	clear or 10x	tR: 66/92	n.a.	n.a.	tR: clear	n.a.	+	32	-	+	n.a.	n.a.
Housman # 235	C	2004	5	19,5 22x	Excimer laser 308 nm. (100-350 mJ/cm2 dependent on MED), 2x/W until 7.5 W then maintenance therapy	after 8.5 W	tR: 100% (5/5) mPR: 83%	n.a.	n.a.	tR: target lesions: PASI 75 mPR: mean PASI reduction of target lesions	n.a.	+	0	n.a.	-	n.s.	n.a.

1) **Pretreatment with salicylic acid 6%**

2) **Seven of nine cleared patients were followed up for one year**

3) **All six cleared patients were followed up for one year**

SOP for creation of European Dermatology Guidelines

Step	Responsible	Task	Months duration
1	EDF Guidelines Committee (EDF-GC) *	Decision of topic of specific guideline	∅
2	EDF Board	Confirmation of the choice and level of guideline (S1, S2 or S3) plus suggestion to the Guideline Committee of potential chairmen and subcommittee members.	0,5
3	EDF-GC	Foundation of subcommittee for specific guidelines. Nomination of EDF members (50 %) as well as identification of possible EADV members (25 % of members for the subcommittee) who could work within the subcommittee. Chairman of EDF guideline committee asks EADV president for approval. Finally nomination of a chairperson of the subcommittee by the group.	at EDF Meeting
4	EDF Guidelines Subcommittee (EDF-GSubC)	Development of a business plan (see attachment)	1
5	EDF Board	Confirmation of business plan and signature of the contract for financial support of guideline	1
6	EDF-GSubC	Identify all existing guidelines for the specific guideline (active process: literature survey plus contact to Dermatological Societies)	1
7	EDF-GSubC	Select the guidelines with highest quality. Criteria for selection: 1. Availability of strength of evidence 2. Availability of strength of recommendation 3. Evidence of mechanics of literature review (adhere to the recommendations of the Cochrane collaboration. These standards should assure high quality for the systematic literature search as well as for the critical appraisal of the papers. For further information see http://www.cochrane.org/crgprocedures/chapter4/1.htm and documents available at EDF Guidelines Secretariat (Mrs. Janine Schweiger, janine.schweiger@charite.de)	1
8	EDF-GSubC	Identification/nomination of additional 50 % EDF members for the EDF-GSubC from amongst the authors of the best guidelines	0,5
9	Chairperson of EDF-GSubC	Consider involvement of other disciplines and patients´ organisations	1
10	EDF-GSubC	Meet 1. to decide the author of the first draft (normally the chairperson of the subcommittee) and to discuss the present guidelines, their strengths and weaknesses 2. 6 months later to discuss the draft (consensus conference)	6
11	Chairperson of EDF-GSubC	Circulate the guideline draft to national dermatological societies for comments (actual list of societies and their presidents at EDF guidelines secretariat)	2
12	EDF-GSubC	Circulate final version for approval among members of the guideline subcommittee	1
13	EDF-GSubC	Deliver final version to EDF guideline committee chairperson, who forwards it to the EDF-GC	∅
14	EDF-GC	Review and comment guideline	1
15	Chairperson of EDF-GSubC	Send final version to EADV Board and to UEMS for approval	2
16	Chairperson of EDF-GSubC	Send guideline for official approval to UEMS (formal approval)	1
17	EDF secretary	Distribute guideline for in advance information to EDF members and National Dermatological Societies	1
18	EDF	Publication 1. on EDF homepage (by Prof. Lajos Kemeny, responsible for the website) 2. in European dermatological journals (normally in EJD, if already published in another journal, a written permission must be obtained to publish in EJD) 3. If publication in other national and international journals is requested by the respective society, this will be encouraged by the EDF	6

The normal expiry date of a guideline is 3 years after finishing point 17. In well defined exceptions the expiry date may be prolonged up to 5 years.

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* The Guideline Committee consists of the founding members of the EDF guideline work as well as of chairpersons of guidelines subcommittees.