S3 Guideline for the treatment of psoriasis vulgaris, update – Short version part 1 – Systemic treatment


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*Haut- und Allergieklinik, Klinikum Hanau [Department of Dermatology and Allergology, Hanau Medical Center]
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†Dermatologikum Hamburg [Dermatologikum Hamburg]
‡Niedergelassener Dermatologe, Osnabrück [Office-based Dermatologist, Osnabrück]
∥Niedergelassener Dermatologe, Oldenburg [Office-based Dermatologist, Osnabrück]
¶Berolina Klinik, Löhne [Berolina Medical Center, Löhne]
∥Niedergelassener Dermatologe, Mahlow [Office-based Dermatologist, Mahlow]
Summary
The German guideline for the treatment of psoriasis vulgaris was updated using GRADE methodology. The guideline is based on a systematic literature review completed on December 1, 2016, and on a formal consensus and approval process. The first section of this short version of the guideline covers systemic treatment options considered relevant by the expert panel and approved in Germany at the time of the consensus conference (acitretin, adalimumab, apremilast, cyclosporine, etanercept, fumaric acid esters, infliximab, methotrexate, secukinumab and ustekinumab). Detailed information is provided on the management and monitoring of the included treatment options.

Evidence search and assessment
The literature search was performed on September 30, 2016, using Embase Ovid (1980 to September 29, 2016), MEDLINE Ovid (1946 to the third week of September 2016), MEDLINE(R) In-Process & Other Non-Indexed Citations Ovid (September 29, 2016) databases and the Cochrane Central Register of Controlled Trials CENTRAL. Autoalerts were screened up to December 1, 2016. The evidence was assessed according to the methods recommended by Cochrane, including GRADE methodology [1].

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

Introduction
This is a short version of the German evidence- and consensus-based (S3) guideline for the treatment of psoriasis vulgaris. The long version is available at www.awmf.org. Please refer to the long version for the following sections: introduction, aims of the guideline, indicators of quality of care, instructions on using the guideline, detailed description of methodology, definition of the severity of psoriasis vulgaris, quality of life, treatment aims, treatment costs, benefit-risk assessment and basic therapy. The sections on biosimilars, climate therapy, psychosocial therapy, topical therapy, phototherapy, interfaces between different providers and sectors of care, and references can also be found in the long version. The guideline is an update, and some sections of the text have been taken from the previous version of the guideline from 2011.

Methods
At their initial meeting, the authors of the guideline agreed on the main points that required updating. It was decided to include new sections on “Special patient populations” and “Special treatment situations” and not to update the sections on topical therapy, phototherapy, climate therapy and psychosocial therapy as major changes were not anticipated in the content of the recommendations in these areas. However, the importance of these therapies continues unchanged, and the recommendations are included in the appendix of the long version. Phototherapy (PUVA, UV) should be regarded as a separate treatment category and is not considered a “systemic therapy”.

Treatment recommendation
At present, there is no distinct stepwise procedure or strict clinical algorithm for the treatment of psoriasis vulgaris. The criteria for selecting appropriate therapies are complex.

Key recommendations formulated in the text are augmented by symbols representing the strength of the treatment recommendation. The following symbols were used to standardize the treatment recommendations:
### Consensus procedure

Consensus was reached by a nominal group process in a consensus conference (moderator: Prof. Dr. Berthold Rzany, MSc, AWMF guideline consultant).

A detailed description of the methodology used to develop the guideline and declarations of interest can be found in the methods report (www.psoriasis-leitlinie.de).

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**Figure 1** Overview of evaluated treatment options for chronic psoriasis vulgaris (the order is alphabetical and does not indicate priority).
Updates/validity
This is an update of the S3 guideline for the treatment of psoriasis vulgaris published in 2011 [2]. Some text passages have been included without change. The current version is valid until December 31, 2020.

Therapeutic options and treatment evaluation
Figure 1 provides an overview of evaluated treatment options for chronic psoriasis vulgaris.

Systemic therapies
The “tabular evaluation” provided in Table 1 is intended to serve as a rough guide for assessing therapeutic options. Cumulative calculations of individual aspects in the overall assessment are not possible and cannot be used for a conclusive evaluation of a given treatment option. Each column should be viewed separately. The evaluation may vary significantly on a case-by-case basis. Assessments are based on a literature review and expert opinion. For further explanations, please refer to the long version.

Table 1  Quick reference table for assessing systemic treatment options.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Quality of evidence (GRADE)</th>
<th>Safety/tolerability of induction therapy</th>
<th>Safety/tolerability of maintenance therapy</th>
<th>Feasibility (patient)</th>
<th>Feasibility (doctor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin**</td>
<td>0/++</td>
<td>No comparison available</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>+++*</td>
<td>⊕⊕⊕⊕</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Apremilast</td>
<td>+</td>
<td>⊕⊕⊕⊕</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>+*</td>
<td>⊕⊕⊕</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Etanercept</td>
<td>++*</td>
<td>⊕⊕⊕</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Fumarate</td>
<td>+*</td>
<td>⊕⊕⊕</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Infliximab</td>
<td>++++</td>
<td>⊕⊕⊕</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+/−</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>+</td>
<td>⊕⊕</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>++++</td>
<td>⊕⊕⊕</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>++++</td>
<td>⊕⊕⊕</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

* up to ++++: assessment of efficacy taking into account PASI 75 results (placebo and head-to-head trials) and expert opinion.
*Expert opinion taken into account.
**For women of childbearing age, treatment with acitretin is generally not recommended.

Acitretin

<table>
<thead>
<tr>
<th>Treatment recommendations</th>
<th>Consensus strength</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin may be considered for induction therapy of moderate to severe psoriasis vulgaris.</td>
<td>→ Consensus Evidence-and consensus-based</td>
<td></td>
</tr>
<tr>
<td>Acitretin cannot be recommended in women of child-bearing age with psoriasis vulgaris.</td>
<td>↓ Strong consensus Clinical consensus point</td>
<td></td>
</tr>
</tbody>
</table>

Acitretin summary table

<table>
<thead>
<tr>
<th>Approval of acitretin in Germany</th>
<th>1992 (psoriasis vulgaris)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended initial dose</td>
<td>Initial dose: 20–30 mg acitretin per day for 2–4 weeks. After the initial phase, the dose can be increased to a maximum of 75 mg acitretin per day in individual cases.</td>
</tr>
</tbody>
</table>
Recommended maintenance dose

Individual dose depends on outcome and tolerability. Maintenance dose: 25–50 mg per day

Onset of clinical effect

Insufficient data [3]

Selection of main contraindications

– Renal and hepatic damage
– Severe hyperlipidemia
– Women of child-bearing age who plan to have children
– Pregnancy
– Breast-feeding
– Use of contact lenses

Selection of important ADRs

– Hypervitaminosis A such as cheilitis, xerosis, epistaxis, alopecia, increased skin fragility, elevation of triglyceride and cholesterol levels

Selection of important drug interactions

Tetracyclines, phenytoin, systemic retinoids or high-dose vitamin A, methotrexate, alcohol, minipill

Miscellaneous

Contraception required until three years after discontinuation in women of child-bearing age

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Table 2 Important adverse reactions associated with acitretin.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Hypervitaminosis A (e.g., associated with xerosis of the skin and mucous membranes), cheilitis, elevated transaminases and AP, elevated serum levels of triglycerides and cholesterol</td>
</tr>
<tr>
<td>Common</td>
<td>Conjunctivitis (caution: contact lenses), effluvium, photosensitivity</td>
</tr>
<tr>
<td>Occasional</td>
<td>Muscle, joint and bone pain</td>
</tr>
<tr>
<td>Rare</td>
<td>Gastrointestinal symptoms, hepatitis, jaundice, bone changes with long-term therapy</td>
</tr>
<tr>
<td>Very rare</td>
<td>Pseudotumor cerebri, night blindness</td>
</tr>
</tbody>
</table>

A selection of important ADRs can be found in Table 2.

Prevention/management of ADRs

If adverse reactions occur, the dosage can be adjusted or divided into two doses per day. See also Table 3.

Main contraindications/limitations of use

Absolute contraindications

– Severe renal or hepatic dysfunction
– In women of child-bearing age: pregnancy, breast-feeding, desire to have children or when reliable contraception cannot be adequately ensured up to three years after discontinuation of treatment

Important relative contraindications

– Alcohol abuse [5]
– Overt diabetes mellitus
– Wearing contact lenses
– Childhood
– History of pancreatitis
– Use of drugs to control hyperlipidemia
– Concomitant use of tetracyclines or methotrexate

Drug interactions

See Summary of Product Characteristics.

– Tetracyclines (tetracycline, doxycycline and minocycline) and acitretin may lead to increased intracranial pressure (pseudotumor cerebri). They should not be used concomitantly with acitretin.
– When used concomitantly, acitretin can displace phenytoin from plasma protein-binding sites.

Dosage and dosing regimen

An initial dose of 25 mg (25 mg once a day) or 30 mg acitretin (10 mg three times a day) over a period of two to four weeks is used in adults. The dose is then adjusted according to tolerability and individual response. The daily maintenance dose is generally between 25–50 mg and can be increased to a maximum of 75 mg (25 mg three times a day).

At the optimal dose, patients will develop slightly dry lips. This can be useful in determining the optimal dose [4].

Summary of the evidence

See long version.

Adverse drug reactions/safety

See Summary of Product Characteristics.

Treatment with an effective dose is often associated with many undesirable effects, most of which are reversible, with the exception of hyperostosis. In all studies, the reported adverse drug reactions were dose-dependent. Cheilitis occurs in nearly 100 % of treated patients. Teratogenicity significantly limits the options for treating women of child-bearing age. High-dose therapy with retinoids can cause mood changes, with symptoms such as irritability, aggressiveness and depression.
Concomitant use of high doses of vitamin A and other systemic retinoids is not advisable.

When used concomitantly with methotrexate, there is an increased risk of toxic hepatitis.

The contraceptive effect of the low-dose progesterone pill (minipill) may be reduced by concomitant use of acitretin.

Notes on use

The capsules should preferably be taken during a fatty meal or with whole milk. To ensure that the patient is not pregnant, treatment should be started on the second or third day of the menstrual cycle if this has been preceded by reliable contraception for at least one month. In some patients, acitretin is converted to etretinate, which is facilitated by alcohol consumption. Alcohol is therefore prohibited in women of child-bearing age while they are taking the drug and for two months after discontinuation of treatment. Given that acitretin may be converted to etretinate, women of child-bearing age must continue to use contraception until three years after discontinuation of treatment.

Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.

Pretreatment measures

– Rule out alcohol abuse
– Inform the patient about the teratogenic risk and need for prolonged contraception until three years after the conclusion of treatment (verbal and written informed consent with signature)
– Inform the patient that blood must not be donated during treatment and up to three years thereafter.
– Ask about bone and joint pain
– For laboratory tests, see Table 4

Measures during treatment

– Long-term treatment (roughly one to two years): if there are any symptoms, radiographic imaging of the spine and joints is recommended to rule out potential ossification.
– For women of child-bearing age: effective contraception and avoidance of alcohol consumption during treatment.
– Reminder that blood must not be donated during and until three years after treatment.
– For laboratory tests, see Table 4
– Patients with risk factors for cardiovascular disease, e.g., hypertension, should be monitored regularly.

Posttreatment measures

– Remind patients that they must not donate blood until three years after discontinuation of treatment.
– Effective contraception* in women of child-bearing age until three years after treatment.
– For women of child-bearing age: avoid alcohol consumption until two months after discontinuation of treatment.

Table 4 provides an overview of laboratory tests for acitretin therapy recommended by the expert group.

Overdose/management of overdose/feasibility/costs and special considerations

See long version.
Adalimumab

<table>
<thead>
<tr>
<th>Treatment recommendations</th>
<th>Consensus strength</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab is recommended for induction therapy of moderate-to-severe psoriasis vulgaris, especially if other forms of therapy have failed, are not tolerated or are contraindicated.</td>
<td>Strong consensus</td>
<td>Evidence- and consensus-based</td>
</tr>
</tbody>
</table>

Adalimumab summary table

<table>
<thead>
<tr>
<th>Approval of adalimumab in Germany</th>
<th>2005 (psoriatic arthritis)</th>
<th>2007 (psoriasis vulgaris)</th>
<th>2015 (psoriasis vulgaris in children aged 4 and older)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended initial dose</td>
<td>80 mg subcutaneously</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended maintenance dose</td>
<td>40 mg subcutaneously every 2 weeks, starting 1 week after the induction dose; if there is an inadequate response after 16 weeks, 40 mg can be given subcutaneously every week</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Onset of clinical effect  | PASI 75 response in 25 % of patients after 4.6 weeks [3]

Selection of main contraindications  | Active tuberculosis or other serious infection, NYHA class III/IV heart failure

Selection of important ADRs  | Reactions at the injection site, serious infections, hair loss, autoimmune phenomena

Selection of important drug interactions  | Anakinra (IL1-R antagonist), abatacept

Miscellaneous  | TNF-alpha antagonist Approval for children aged 4 and older

Dosage and dosing regimen

Adalimumab is administered by subcutaneous injection. According to the dosing regimen, a loading dose of 80 mg is given at the beginning of treatment, 40 mg one week later, and then 40 mg every other week. The dose is not adjusted for obese patients (> 100 kg).

If the response is insufficient after 16 weeks of treatment, the dose can be increased to 40 mg every week. If there is no improvement on the increased dose after another eight weeks, treatment should be discontinued. If an adequate response is achieved, the dose should be reduced to 40 mg every other week.
Summary of the evidence

See long version.

Adverse drug reactions/safety

See Summary of Product Characteristics.

In placebo-controlled studies, reactions at the injection site were the most commonly reported adverse event (adalimumab: 20% of patients; placebo: 14% of patients). A burning sensation that can occur during injection was reduced by altering the excipients, including not using citrate.

Adalimumab therapy is associated with an increased rate of infections. Rarely reported hematological effects include thrombocytopenia and leukopenia. Rare severe allergic reactions include rash, urticaria, pruritus, dyspnea, chest tightness, as well as swelling of the mouth, face, lips or tongue.

Treatment with adalimumab may be associated with the induction of autoantibodies (ANA, anti-dsDNA antibodies) and the onset of a lupus-like syndrome. In such cases, treatment should be discontinued immediately.

Malignant tumors can occur very rarely. Anti-drug antibodies (ADA) may develop during treatment with adalimumab, which may be associated with a loss of effectiveness (secondary treatment failure).

Notes on use

Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.

Pretreatment measures

- Rule out acute infection
- Tuberculosis must be definitively ruled out. See long version, section on “Tuberculosis”
- Contraception must be ensured, and pregnancy ruled out in women of child-bearing age
- Patients should be informed that any infection may run an atypical and more severe clinical course and that they should seek medical attention as early as possible if an infection is suspected.

Measures during treatment

- Monitoring for infection; if infection is suspected, treatment should be discontinued, at least temporarily.

Posttreatment measures

- None

Table 5 provides an overview of the laboratory tests for adalimumab therapy recommended by the expert group.

Table 5  Laboratory tests in patients on adalimumab.

<table>
<thead>
<tr>
<th>Point in time</th>
<th>Diagnostic tests</th>
<th>Before treatment</th>
<th>After 4 weeks</th>
<th>After 12 weeks</th>
<th>Then every 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>AST, ALT, GGT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HIV and hepatitis C serology*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test (urine)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If infection is suspected, see pretreatment measures

According to the Summary of Product Characteristics, no laboratory tests are currently suggested during treatment with adalimumab. The guideline authors recommend the tests listed above. Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.

*As indicated by patient history, clinical signs or other laboratory test results.
Overdose/management of overdose/feasibility/costs and special considerations

See long version.

Apremilast

<table>
<thead>
<tr>
<th>Treatment recommendations</th>
<th>Consensus strength</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apremilast may be recom-</td>
<td>↑ Strong</td>
<td>Evidence-</td>
</tr>
<tr>
<td>mended for induction</td>
<td>consensus</td>
<td>and con-</td>
</tr>
<tr>
<td>therapy of moderate to</td>
<td></td>
<td>sensus-ba-</td>
</tr>
<tr>
<td>severe psoriasis vulgaris,</td>
<td></td>
<td>sed</td>
</tr>
<tr>
<td>especially if other forms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>of therapy have failed,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>are not tolerated or are</td>
<td></td>
<td></td>
</tr>
<tr>
<td>contraindicated.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Apremilast summary table

<table>
<thead>
<tr>
<th>Approval of apremilast in Germany</th>
<th>2015 (moderate to severe psoriasis vulgaris and psoriatic arthritis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended initial dose</td>
<td>10 mg per day according to the dosing regimen below this table</td>
</tr>
<tr>
<td>Recommended maintenance dose</td>
<td>60 mg per day (30 mg twice a day) according to the dosing regimen (see long version)</td>
</tr>
<tr>
<td>Onset of clinical effect</td>
<td>PASI 75 response in 25 % of patients after 10.9 weeks with 30 mg twice a day [6]</td>
</tr>
<tr>
<td>Selection of main contraindica-</td>
<td>- Pregnancy and breast-feeding</td>
</tr>
<tr>
<td>tions</td>
<td>- Diarrhea</td>
</tr>
<tr>
<td>Selection of important ADRs</td>
<td>- Nausea</td>
</tr>
<tr>
<td>Selection of important drug inter-</td>
<td>- Suicidal ideation</td>
</tr>
<tr>
<td>actions</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
</tbody>
</table>

Dosage and dosing regimen

The dose of apremilast is increased to 60 mg according to the dosing regimen (see long version).

If renal function is severely impaired, the recommended dose is 30 mg once a day in the morning.

Summary of the evidence

See long version.

Adverse drug reactions/safety

See long version and Summary of Product Characteristics.

Among the adverse drug reactions, diarrhea in particular is of significant practical relevance. Just under one-fifth of patients develop diarrhea, usually in the first week during dose escalation. Clinical symptoms are frequently rather mild, with several thin bowel movements per day. If appropriately informed, the majority of patients do not deviate from the planned dosing regimen. The diarrhea symptoms usually cease spontaneously within the first month of treatment. In cases associated with more severe diarrhea, use of loperamide has been shown to be effective.

Some patients (approximately 15 %) experience significant weight loss (5–10 %) within the first months of apremilast therapy. However, this phenomenon is not a contraindication for continuing treatment with apremilast.

There have been occasional reports of suicidal ideation and behavior (with or without a history of depression) both in clinical studies and following market introduction (frequency ≥ 1/1,000 to ≤ 1/100). Cases of completed suicide in patients treated with apremilast have been reported following market introduction.

Main contraindications/limitations of use

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pregnancy and breast-feeding</td>
</tr>
</tbody>
</table>

Important relative contraindications

- For patients with a history of psychiatric symptoms or patients taking medications likely to cause psychiatric symptoms, the benefits of apremilast treatment should be carefully weighed against the risks.
- Underweight patients
- Children and adolescents

Drug interactions

Patients should not take apremilast if they are taking strong inducers of CYP3A4 (e.g., rifampicin, phenytoin, carbamazepine, phenytoin and St. John’s wort) as this leads to a relevant decrease in apremilast levels.
Notes on use

Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.

Pretreatment measures
– For laboratory tests see Table 6
– Rule out pregnancy and initiate contraception in women of child-bearing age.
– For patients with a history of psychiatric symptoms or patients taking medications likely to cause psychiatric symptoms, the benefits of apremilast treatment should be carefully weighed against the risks.
– Measure body weight

Measures during treatment
– Interruption of treatment if the patient becomes pregnant
– Discontinuation of treatment if there are new-onset psychiatric symptoms or exacerbation of existing symptoms or suicidal ideation or attempted suicide
– Contraception
– Weight should be monitored in underweight patients (BMI < 18.5 kg/m²)
– For laboratory tests see Table 6

Posttreatment measures
– None

Table 6 provides an overview of the laboratory tests for apremilast therapy recommended by the expert group.

Feasibility and costs
See long version.

Cyclosporine

<table>
<thead>
<tr>
<th>Treatment recommendations</th>
<th>Consensus strength</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine may be recommended for induction therapy of moderate to severe psoriasis vulgaris.</td>
<td>Strong consensus</td>
<td>Evidence-and consensus-based</td>
</tr>
<tr>
<td>A combination of cyclosporine and topical preparations to treat moderate to severe psoriasis vulgaris may be recommended.</td>
<td>Strong consensus</td>
<td>Evidence-and consensus-based</td>
</tr>
</tbody>
</table>

Cyclosporine summary table

<table>
<thead>
<tr>
<th>Approval of cyclosporine in Germany</th>
<th>1983 (transplantation medicine)</th>
<th>1993 (psoriasis vulgaris)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended initial dose</td>
<td>2.5–3 (max. 5) mg/kg body weight</td>
<td></td>
</tr>
<tr>
<td>Recommended maintenance dose</td>
<td>Intermittent therapy (each cycle 8–16 weeks) with a dose reduction at the end of induction therapy (e.g., 0.5 mg/kg body weight every 14 days) or continuous long-term therapy with dose reduction, e.g., by 50 mg every 4 weeks after week 12 and dose increase by 50 mg in case of recurrence</td>
<td></td>
</tr>
<tr>
<td>Onset of clinical effect</td>
<td>PASI 75 response in 25 % of patients after 6 weeks (&lt;5 mg/kg body weight) [3]</td>
<td></td>
</tr>
</tbody>
</table>
### Guidelines S3 Psoriasis guideline

#### Selection of main contraindications

**Absolute:**
- Relevant renal impairment
- Uncontrolled arterial hypertension
- Active tuberculosis or other serious infection
- Relevant malignancy (current or past, especially hematological disorders and cutaneous malignancies, except for basal cell carcinoma)

**Relative:**
- Relevant hepatic impairment
- Pregnancy and breastfeeding
- Concomitant use of substances that interact with cyclosporine
- Simultaneous phototherapy or previous PUVA therapy with a cumulative dose > 1,000 J/cm²
- Concomitant use of other immunosuppressants, retinoids or previous long-term therapy with methotrexate (MTX)

#### Miscellaneous

- Calcineurin inhibitors
- In transplant patients, increased risk of lymphoproliferative disorders
- In psoriasis patients, excessive phototherapy can lead to increased risk of squamous cell carcinoma
- Only moderately effective for psoriatic arthritis and not approved
- Has also been successfully used in children with chronic inflammatory diseases

#### Selection of important ADRs

- Renal impairment
- Increase in blood pressure
- Hepatic impairment
- Nausea
- Loss of appetite
- Vomiting
- Diarrhea
- Hypertrichosis
- Gingival hyperplasia
- Tremor
- Fatigue
- Paresthesia

#### Selection of important drug interactions

The possibility of multiple interactions should be considered (see long version)

#### Dosage and dosing regimen

A standard dose for treatment initiation is 2.5–3 mg/kg body weight. If there is an inadequate response to the initial dose of 2.5–3 mg/kg body weight after four to six weeks, the dose may be increased to a maximum of 5 mg/kg body weight.

For other dosing regimens, please see the long version.

#### Summary of the evidence

See long version.

#### Adverse drug reactions/safety

See long version and Summary of Product Characteristics.

The included studies, most of which investigated short-term treatment (induction therapy), reported various adverse effects on cyclosporine therapy. Whenever various doses were studied, the rate of adverse effects was usually clearly dose-dependent [7].

The most commonly reported adverse effects included:

##### Kidneys/blood pressure

- Increase in serum creatinine (by 5–30 % on average, and by > 30 % in up to 20 % of patients)
- Drop in creatinine clearance (up to 20 % on average)
- Increased urea (in up to 50 % of patients)
- Decrease in magnesium levels (by 5–15 % on average)
- Increased uric acid (in about 5 % of patients)
- Arterial hypertension (in about 2–15 % of patients)

##### Liver/gastrointestinal tract

- Gastrointestinal symptoms (nausea, diarrhea, flatulence, and others, in about 10–30 % of patients)
– Increase in bilirubin (in about 10–80 % of patients)
– Increase in transglutaminases (up to 30 % of patients)
– Gingival hyperplasia (up to 15 % of patients)

**Other**
– Paresthesia (up to 40 % of patients)
– Muscle pain (in about 10–40 % of patients)
– Headache (in 10–30 % of patients)
– Tremor (in about 2–20 % of patients)
– Hypertrichosis (in < 5 % of patients)

**Main contraindications/limitations of use**

**Absolute contraindications**
– Relevant renal impairment
– Inadequately controlled hypertension
– Active tuberculosis or other serious infection
– Past or current malignancy (possible exception: adequately treated basal cell carcinoma, squamous cell carcinoma in situ)

**Important relative contraindications**
– Prior potentially carcinogenic therapies (e.g., arsenic, PUVA > 1,000 J/cm²)
– Infection- or drug-induced psoriasis (e.g., beta-blockers, lithium, antimalarial drugs)
– Relevant liver disease
– Hyperuricemia
– Hyperkalemia
– Concomitant treatment with nephrotoxic drugs (see drug interactions)
– Concomitant phototherapy (SUP, PUVA)
– Concomitant use of other immunosuppressants (except for topical therapy)
– Concomitant use of retinoids or treatment with retinoids in the last four weeks before planned initiation of cyclosporine
– Drug or alcohol abuse
– Prior long-term methotrexate (MTX) therapy
– Pregnancy
– Breast-feeding
– Vaccination with live vaccines
– Epilepsy
– Current treatment with castor oil-based preparations

**Drug interactions**

The availability of cyclosporine depends especially on the activity of the hepatic enzyme cytochrome P450-3A4 (CYP3A4) and on intestinal P-glycoprotein. There is a large number of drug interactions.

Please refer to the long version for details.

**Notes on use**

**Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.**

**Pretreatment measures**

**General measures**
– Patient history including past and current comorbidities (e.g., severe infections, malignancy, kidney and liver disease), concomitant medication (see drug interactions)

**Specific measures**
– If there is a corresponding history or clinical or laboratory signs, HIV infection and hepatitis C should be ruled out.
– Rule out hepatitis B
– Screening for potentially malignant skin lesions
– Signs of existing infection
– Measure blood pressure at two different points in time

**Patient education**
– Patients should be informed that any infection may run an atypical and more severe clinical course and that they should seek medical attention as early as possible if an infection is suspected.
– Drug interactions (also inform other treating physicians about the treatment)
– Ensure reliable contraception and rule out pregnancy in women of child-bearing age (Caution: decreased efficacy of progesterone-based contraceptives)
– Avoid excessive exposure to sunlight, especially with long-term use; use of sunscreen

**Measures during treatment**

**Interview/examination**
– Status of skin and mucous membranes (e.g., increased body hair, gingival hyperplasia, rule out skin cancer)
– Signs of existing infection
– Gastrointestinal symptoms and neurological symptoms
– Repeat recommendation with respect to UV protection
– Check co-medications
– Measure blood pressure
– With uncomplicated low-dose long-term therapy (2.5–3 mg/kg body weight daily), follow-up intervals may subsequently be extended to three months.
– Shorter intervals are required, for example, in patients with risk factors, in case of a dose increase, and with use of drugs that may affect metabolism or cause drug interactions
– Measure creatinine clearance if plasma creatinine levels appear abnormal
– In select patients on intermittent or short-term treatment, less frequent follow-up may suffice (e.g., regular measurement of blood pressure and creatinine levels)
– Measurement of cyclosporine levels may occasionally be advisable, especially if non-compliance or toxicity due to drug interactions are suspected

**Posttreatment measures**
– None
Table 7 provides an overview of the laboratory tests for cyclosporine therapy recommended by the expert group.

**Overdose/management of overdose**
See long version.

**Feasibility and costs**
See long version.

### Etanercept

<table>
<thead>
<tr>
<th>Treatment recommendations</th>
<th>Consensus strength</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept at a dose of 50 mg (once) may be recommended for induction therapy of moderate to severe psoriasis vulgaris, especially if other forms of therapy have failed, are not tolerated or are contraindicated.</td>
<td>↑ Consensus</td>
<td>Evidence-based</td>
</tr>
</tbody>
</table>

**Etanercept summary table**

<table>
<thead>
<tr>
<th>Approval of etanercept in Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002 (psoriatic arthritis)</td>
</tr>
<tr>
<td>2004 (psoriasis vulgaris)</td>
</tr>
<tr>
<td>2008 (psoriasis vulgaris in children)</td>
</tr>
</tbody>
</table>

**Dosage and dosing regimen**

The etanercept dose approved for the treatment of psoriasis vulgaris in adults is 25 mg twice a week or alternatively 50 mg once a week. If the psoriasis is highly active or in overweight patients, 50 mg twice a week can initially be given for up to twelve weeks, followed by a dose of 25 mg twice a week or 50 mg once a week.
Summary of the evidence

See long version.

Adverse drug reactions/safety

See Summary of Product Characteristics.

The most commonly reported adverse drug reactions are local injection site reactions. The risk of serious infections is increased on anti-TNFα therapy. The incidence of malignancy in patients given etanercept versus a comparison group was similar to the rates and incidence expected for the study population. The number of patients on anti-TNFα therapy who developed lymphoma was slightly higher than in the control group. Adverse hematological effects, demyelinating diseases and autoimmune disorders are class effects of TNF blockers and have occurred with etanercept as well as with other TNFα inhibitors.

Because of the pharmacokinetics of etanercept, no dose adjustment is required in patients with impaired renal and hepatic function. No elevated etanercept levels were found in patients on etanercept therapy with acute renal or liver failure. Etanercept should be used with caution in patients with moderate to severe alcoholic hepatitis.

Main contraindications/limitations of use

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>– NYHA class III–IV heart failure</td>
</tr>
<tr>
<td>– Active tuberculosis or other serious infections</td>
</tr>
</tbody>
</table>

Important relative contraindications

– Demyelinating diseases
– Malignancy (except for basal cell carcinoma) and lymphoproliferative disorders or a history thereof
– Pregnancy and breast-feeding
– Vaccination with live vaccines

Table 8 Laboratory tests in patients on etanercept.

<table>
<thead>
<tr>
<th>Point in time → Diagnostic tests ↓</th>
<th>Before treatment</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Every 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AST, ALT, GGT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hepatitis B serology</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV and hepatitis C serology*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test (urine)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If infection is suspected, see pretreatment measures

According to the Summary of Product Characteristics, no laboratory tests are currently suggested during treatment with etanercept. The guideline authors recommend the tests listed above. Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.

*As indicated by patient history, clinical signs or other laboratory test results.

Drug interactions

Combined use of etanercept and anakinra (IL1-R antagonist) or abatacept is not recommended.

Notes on use

Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.

Pretreatment measures

General measures
– Rule out acute infection
– Tuberculosis must be definitively ruled out. See long version, section on “Tuberculosis”

Specific measures
– Ensure reliable contraception and rule out pregnancy in women of child-bearing age
– Patients should be informed that any infection may run an atypical and more severe clinical course and that they should seek medical attention as early as possible if an infection is suspected.

Measures during treatment
– Monitor for infection; if infection is suspected, treatment should be interrupted, at least temporarily.
– Discontinue treatment if the patient becomes pregnant

Posttreatment measures
– None

Table 8 provides an overview of the laboratory tests for etanercept therapy recommended by the expert group.

Overdose/management of overdose

No dose-limiting toxicity was observed in clinical studies of patients with rheumatoid arthritis [8]. There is no known antidote to etanercept.
Feasibility and costs

See long version.

Fumaric acid esters

<table>
<thead>
<tr>
<th>Treatment recommendations</th>
<th>Consensus strength</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with fumaric acid esters may be recommended for induction therapy of moderate to severe psoriasis vulgaris.</td>
<td>↑ Strong consensus</td>
<td>Evidence- and consensus-based</td>
</tr>
</tbody>
</table>

Fumaric acid esters summary table

| Approval of fumaric acid esters in Germany | 1994 (psoriasis vulgaris, moderate to severe) |
| Recommended initial dose | According to recommended dosing regimen |
| Recommended maintenance dose | Individual dose adjustment |
| Onset of clinical effect | Insufficient data [3] |
| Selection of main contraindications | – Severe gastrointestinal diseases such as gastric and duodenal ulcers – Severe liver or kidney disease |
| Selection of important ADRs | – Gastrointestinal symptoms – Flushing – Lymphopenia – Eosinophilia |
| Selection of important drug interactions | Methotrexate, retinoids, psoralens, cyclosporine, immunosuppressants, cytostatic agents and drugs with a known harmful effect on the kidneys must not be used concomitantly with fumaric acid esters |

Dosage and dosing regimen

The standard clinical procedure consists of slow dose escalation according to an established dosing regimen (Table 9). The gradual dose increase is intended to improve tolerability, especially with regard to gastrointestinal symptoms.

The dose must be adjusted individually depending on the response to treatment and occurrence of adverse effects. The recommended maximum dose is 1.2 g per day = six Fumaderm® tablets; however, effective treatment does not always require this dose. Most patients treated with fumaric acid esters need between two and four Fumaderm® tablets per day. The dose is increased until an adequate clinical response is obtained. The individual maintenance dose is subsequently established by gradual dose reduction.

Fumaric acid ester treatment may be discontinued abruptly without any rebound effects or pustular flare-ups.

Fumaderm® contains a mixture of fumaric acid esters, the main ingredient being dimethyl fumarate.

Summary of the evidence

See long version.

Adverse drug reactions/safety

See long version and Summary of Product Characteristics.

Gastrointestinal complaints (in up to 60 % of patients, especially in the first weeks of treatment) and flushing are the most common adverse effects associated with fumaric acid ester therapy. Gastrointestinal tolerability can be improved by taking the tablets with milk. Acetylsalicylic acid at a dose of 500 mg may help at the first signs of flushing.

Leukopenia, lymphopenia and eosinophilia are frequently observed during treatment with fumaric acid esters. The dose must be halved if the lymphocyte count falls below 700/μL. If there is no rebound of the lymphocyte count after four weeks, fumaric acid ester therapy must be discontinued. A drop in lymphocytes below 500/μL requires immediate discontinuation of treatment. Patients who develop lymphopenia should be monitored for signs and symptoms of opportunistic infections, especially neurological deficits and cognitive or psychiatric symptoms, which may indicate progressive multifocal leukoencephalopathy (PML). The increase in eosinophils is always transient and usually occurs between weeks four and ten.

Table 9  Dosing regimen for treatment with fumaric acid esters.

<table>
<thead>
<tr>
<th>Week</th>
<th>Fumaderm® initial</th>
<th>Fumaderm®</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-0-1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1-0-1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1-1-1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1-0-0</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1-0-1</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>1-1-1</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>2-1-1</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>2-1-2</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>2-2-2</td>
</tr>
</tbody>
</table>
Renal impairment (proteinuria) is occasionally observed and is generally thought to resolve following dose reduction or discontinuation of the drug. Secondary osteomalacia (Fanconi syndrome) is a very rare complication that requires cessation of fumaric acid ester therapy.

Dose adjustment is not required in elderly patients or individuals with impaired liver function as fumarates are not primarily metabolized through the liver.

Prevention/management of ADRs
If adverse drug reactions occur, the dose should initially be reduced; persistent reactions require treatment discontinuation.

Main contraindications/limitations of use

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Severe hepatic or renal impairment</td>
</tr>
<tr>
<td>– Severe gastrointestinal disease</td>
</tr>
</tbody>
</table>

Important relative contraindications

| – Pregnancy and breast-feeding |
| – Comedication with MTX, retinoids, psoralens, cyclosporine, immunosuppressants, cytostatic agents and drugs with a known deleterious effect on the kidneys |

Drug interactions

Fumaric acid esters can impair renal function. Concomitant use of nephrotoxic substances may therefore be associated with increased toxicity. The Summary of Product Characteristics warns about an interaction with nephrotoxic drugs.

Notes on use

Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.

Pretreatment measures

| – For laboratory tests see Table 10 |

Measures during treatment

| – For laboratory tests see Table 10 |

Posttreatment measures

| – None |

Table 10 provides an overview of the laboratory tests for fumaric acid ester therapy recommended by the expert group.

Feasibility and costs

See long version.

Table 10  Laboratory tests in patients on fumaric acid esters.

<table>
<thead>
<tr>
<th>Point in time → Diagnostic tests ↓</th>
<th>Before treatment</th>
<th>Every 4 weeks</th>
<th>Every 8 weeks from month 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count*</td>
<td>X</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>Liver function tests***</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis****</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Erythrocytes, leukocytes, platelets, CBC with differential
**The current Summary of Product Characteristics requires a CBC with lymphocyte count on a monthly basis; the guideline authors consider 8-week intervals to be sufficient and do not believe that patient safety is improved with more frequent monitoring.
***Transaminase, GGT.
****If repeatedly positive for protein or glucose, Fanconi syndrome should be ruled out.

Infliximab

Treatment recommendations

<table>
<thead>
<tr>
<th>Consensus strength</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑↑ Majority agreement</td>
<td>Evidence- and consensus-based</td>
</tr>
</tbody>
</table>

Infliximab is recommended for induction therapy of moderate to severe psoriasis vulgaris, if other forms of therapy have failed, are not tolerated or are contraindicated.

Infliximab summary table

<table>
<thead>
<tr>
<th>Approval of infliximab in Germany</th>
<th>2004 (psoriatic arthritis)/2005 (psoriasis vulgaris)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended initial dose</td>
<td>5 mg/kg body weight (infusions on day zero and in week two and week six)</td>
</tr>
<tr>
<td>Recommended maintenance dose</td>
<td>5 mg/kg body weight (maintenance therapy: every 8 weeks)</td>
</tr>
<tr>
<td>Onset of clinical effect</td>
<td>PASI 75 response in 25% of patients after 3.5 weeks [3]</td>
</tr>
</tbody>
</table>
Dosage and dosing regimen

The dose required for treatment of psoriasis vulgaris depends on the patient’s body weight. It consists of a single dose of 5 mg/kg body weight at week zero, week two and week six, and then regularly every eight weeks.

Prolonged intervals between infusions increase the likelihood of infliximab antibodies being formed. Infliximab is administered by intravenous infusion, delivered over a period of two hours. If there are no infusion reactions, the time can be shortened to one hour. During the infusion and for one hour thereafter, the patient must be monitored with emergency equipment readily available in case that there is an infusion reaction.

Summary of the evidence

See long version.

Adverse drug reactions / safety

See Summary of Product Characteristics.

There is a large body of data on the safety of infliximab in patients with chronic inflammatory bowel disease and arthritis. While these safety data can generally be extrapolated to psoriasis vulgaris, prior treatment of psoriasis patients (UVB, PUVA) may lead to as yet unidentified adverse drug reactions or risks that must be taken into account.

Infusion reactions

Acute infusion reactions are common. These are usually mild and include chills, headache, flushing, nausea, dyspnea or infiltration at the infusion site. The likelihood of an infusion reaction is increased in patients with anti-infliximab antibodies. However, anaphylactoid reactions may also occur irrespective of anti-infliximab antibodies. Patient monitoring with emergency equipment readily available is required during and for an hour after the infusion. Serum sickness can develop three to twelve days thereafter.

Re-initiation of the drug after a prolonged treatment-free interval may cause arthralgia, myalgia, angioedema and other acute reactions.

Moderate infusion reactions can be mitigated or even prevented by prior administration of an antihistamine [9]. Production of infliximab antibodies can be reduced by use of low-dose MTX (5–10 mg/week) [10, 11].

Infections

Infliximab therapy has been associated with severe infections including sepsis, sometimes even fatal. Patients with obvious, clinically relevant infections should therefore not be treated with infliximab. There have also been rare cases of opportunistic infections, including listeriosis, histoplasmosis, cryptococcosis and Pneumocystis carinii pneumonia. Reactivation and subsequent generalization of preexisting latent tuberculosis has been reported in patients on infliximab therapy.

Cardiac effects

Infliximab has been associated with exacerbation of preexisting heart failure. Infliximab must therefore not be used in patients with NYHA class III–IV heart failure.

Demyelinating diseases

As with other TNF-α blockers, isolated cases of demyelinating diseases of the central nervous system have occurred in association with infliximab. Given that multiple sclerosis may be exacerbated by infliximab, patients with multiple sclerosis should therefore receive infliximab therapy only after carefully weighing risks and benefits.

Hepatotoxicity

There have been isolated reports of severe liver damage on infliximab treatment, including fatal liver failure. These were associated with hepatitis B infection and occurred within two weeks until more than a year after treatment initiation. In psoriasis patients, there have only been reports of increases in transaminase levels but not of severe liver damage. Infliximab should be discontinued if jaundice occurs or if there is a significant deterioration of liver function tests.

Hematological changes

Leukopenia, neutropenia, thrombocytopenia and pancytopenia, some with fatal outcome, have been reported in patients
with rheumatoid arthritis or Crohn’s disease who were on infliximab. If the blood count is abnormal, patients should be clinically monitored, and infliximab should be discontinued, if necessary.

The number of cases of lymphoma in patients treated with anti-TNF-α antibodies was slightly higher than in the control group. The risk of other malignancies was not increased relative to the risk in the control group. It is not known whether exposure to infliximab can increase the incidence of these diseases.

Lupus erythematosus-like syndrome

Treatment with infliximab may be associated with the induction of autoantibodies (ANA, anti-dsDNA antibodies) and the onset of a lupus-like syndrome. In such cases, treatment should be discontinued immediately.

Prevention/management of ADRs

When administering the drug, standard emergency equipment should be readily available.

If a severe infection occurs, it is important to bear in mind that – given the long time (six months) required for complete elimination – the immunosuppressant effect of infliximab can last several weeks after the last dose. Simultaneous administration of methotrexate can reduce the formation of anti-infliximab antibodies [10, 11].

Main contraindications/limitations of use

### Absolute contraindications
- NYHA class III–IV heart failure
- Known hypersensitivity to mouse proteins
- Active tuberculosis or other serious infections

### Important relative contraindications
- Malignancy (except for basal cell carcinoma) and lymphoproliferative disorders, including a history thereof
- Live vaccines
- Autoimmune diseases
- Demyelinating diseases
- Pregnancy and breast-feeding

**Drug interactions**

Combined use of infliximab and anakinra (IL1-R antagonist) or abatacept is not recommended.

**Notes on use**

*Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.*

#### Pretreatment measures

- Rule out acute infection
- Tuberculosis must be definitively ruled out. See long version, section on “Tuberculosis”
- Ensure reliable contraception and rule out pregnancy in women of child-bearing age
- Patients should be informed that any infection may run an atypical and more severe clinical course and that they should seek medical attention as early as possible if an infection is suspected.

#### Measures during treatment

- Monitor up to an hour after the infusion
- Monitor for infection; if infection is suspected, treatment should be interrupted, at least temporarily.

#### Posttreatment measures

- None

Table 11 provides an overview of the laboratory tests for infliximab therapy recommended by the expert group.

**Overdose/management of overdose**

Single doses of up to 20 mg/kg body weight were tolerated without any direct toxic effect. In the case of overdose,
the patient should be monitored closely and should receive prompt adequate symptomatic treatment.

Feasibility and costs
See long version.

Methotrexate

<table>
<thead>
<tr>
<th>Treatment recommendations</th>
<th>Consensus strength</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate may be recommended for induction therapy of moderate to severe psoriasis vulgaris.</td>
<td>↑</td>
<td>Strong consensus</td>
</tr>
</tbody>
</table>

Methotrexate summary table

<table>
<thead>
<tr>
<th>Approval of methotrexate in Germany; many different suppliers; tablets or solution for injection</th>
<th>1991 (psoriasis vulgaris)</th>
<th>1992 (psoriasis vulgaris)</th>
<th>2004 (psoriasis vulgaris)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended initial dose</td>
<td>15 mg per week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended maintenance dose</td>
<td>5–20 mg per week depending on the effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset of clinical effect</td>
<td>PASI 75 response in 25 % of patients after 3.2 weeks (≥15 mg) and 9.9 weeks (&lt; 15 mg) [3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection of main contraindications</td>
<td>Hepatic impairment, pregnancy, preexisting tuberculosis or other serious infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection of important ADRs</td>
<td>Hepatic fibrosis/cirrhosis, pneumonia/alveolitis, bone marrow depression, kidney damage, infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection of important drug interactions</td>
<td>Multiple drug interactions (see text)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Dihydrofolate reductase inhibitor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dosage and dosing regimen

For the treatment of psoriasis vulgaris, methotrexate is administered once a week, preferably by parenteral injection. The recommended initial dose is 15 mg, which may be increased to 20 mg per week if there is insufficient response. The dose can be adjusted on an individual basis during long-term therapy. Administration of folic acid (5 mg) 24 hours after the methotrexate dose is recommended, although there is conflicting evidence regarding the benefit of this intervention.

Table 12 Important adverse reactions associated with methotrexate.

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common Nausea, fatigue, vomiting, elevated transaminases, hair loss (reversible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occasional</td>
<td>Fever, headache, depression, infection</td>
</tr>
<tr>
<td>Rare</td>
<td>Bone marrow suppression with leukopenia, thrombocytopenia, agranulocytosis, pancytopenia, liver fibrosis and liver cirrhosis, gastrointestinal ulcers, nephrotoxicity</td>
</tr>
<tr>
<td>Very rare</td>
<td>Interstitial pneumonia, alveolitis</td>
</tr>
</tbody>
</table>

Summary of the evidence

See long version.

Adverse drug reactions/safety

See Table 12, the long version and the Summary of Product Characteristics.

Methotrexate may increase the risk of liver fibrosis and cirrhosis. Risk factors include obesity and diabetes mellitus. Measurement of serum levels of the amino-terminal propeptide of type III procollagen (PIIINP) before and during methotrexate therapy may help detect incipient liver damage. Ultrasound is likewise suitable for detecting methotrexate-induced hepatopathy. Myelosuppression, acute pneumonitis or alveolitis and pulmonary fibrosis can lead to death. Myelosuppression has been repeatedly reported, especially in patients with renal failure. Acute pneumonitis and alveolitis are very rare.

Management of adverse drug reactions

Indications for interrupting treatment include elevated transaminases (more than three times the upper normal limit), anemia, decrease in white blood cell or platelet counts in peripheral blood, increased creatinine levels, acute dyspnea, cough and severe infections.

A drop in white blood cell and platelet levels usually occurs seven to ten days after the last dose. Treatment must be discontinued if any of the following occur: severe leukopenia, diarrhea (dehydration), ulcerative stomatitis, nephrotoxicity or pulmonary toxicity. An increase in MCH (mean corpuscular hemoglobin) is a common side effect and indicates developing megaloblastic anemia. Folic acid supplementation (5 mg) the day after the methotrexate dose can help prevent mild adverse drug reactions.
Main contraindications/limitations of use

**Absolute contraindications**
- Women who are currently planning to have children
- Pregnancy and breast-feeding
- Inadequate contraception
- Known hypersensitivity to methotrexate (e.g., pulmonary toxicity)
- Severe liver disease
- Renal failure
- Active tuberculosis or other serious infection
- Actives peptic ulcer
- Hematological changes (leukopenia, thrombocytopenia, anemia)

**Important relative contraindications**
- Men who are currently planning to have children
- Renal impairment
- Hepatic impairment
- Chronic congestive cardiomyopathy
- Diabetes mellitus
- History of hepatitis
- Poor patient compliance
- Diarrhea
- Gastritis

**Drug interactions**

See Table 13, the Summary of Product Characteristics and the long version.

Antibiotics can affect the intestinal flora and hamper MTX (re)absorption. Folic acid can diminish the effectiveness of MTX.

Caution is required when MTX is administered with other potentially hepatotoxic drugs and alcohol and when vaccination with a live vaccine is carried out.

**Notes on use**

Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.

**Pretreatment measures**

**General measures**
- Rule out acute infection
- Tuberculosis must be definitively ruled out. See long version, section on “Tuberculosis”

**Specific measures**
- Inform the patient about how to take the drug (only one day a week) and about early symptoms of potential adverse effects
- Physical examination, screening for skin lesions typically associated with cirrhosis
- Liver ultrasound if indicated, i.e., if there is a positive history or abnormal findings on physical examination
- Chest X-ray (for later comparison if any pulmonary changes occur during treatment)

**Measures during treatment**
- Consistent contraception in women of child-bearing age
- Laboratory monitoring, see Table 14

---

**Table 13** Drug interactions associated with methotrexate.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced renal elimination of MTX</td>
<td>- Cyclosporine</td>
</tr>
<tr>
<td></td>
<td>- Salicylates</td>
</tr>
<tr>
<td></td>
<td>- Sulfonamides</td>
</tr>
<tr>
<td></td>
<td>- Probenecid</td>
</tr>
<tr>
<td></td>
<td>- Penicillins</td>
</tr>
<tr>
<td></td>
<td>- Colchicine</td>
</tr>
<tr>
<td></td>
<td>- Cyclooxygenase inhibitors (COX inhibitors)</td>
</tr>
<tr>
<td>Increased bone marrow toxicity and gastrointestinal toxicity</td>
<td>- Ethanol</td>
</tr>
<tr>
<td></td>
<td>- Cotrimoxazole</td>
</tr>
<tr>
<td></td>
<td>- Pyrimethamine</td>
</tr>
<tr>
<td></td>
<td>- Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td>- Sulfonamides</td>
</tr>
<tr>
<td></td>
<td>- COX inhibitors</td>
</tr>
<tr>
<td></td>
<td>- Cytostatic agents</td>
</tr>
<tr>
<td>Displacement of MTX from plasma protein binding</td>
<td>- COX inhibitors</td>
</tr>
<tr>
<td></td>
<td>- Probenecid</td>
</tr>
<tr>
<td></td>
<td>- Barbiturates</td>
</tr>
<tr>
<td></td>
<td>- Phenytoin</td>
</tr>
<tr>
<td></td>
<td>- Retinoids</td>
</tr>
<tr>
<td></td>
<td>- Sulfonamides</td>
</tr>
<tr>
<td></td>
<td>- Sulfonylureas</td>
</tr>
<tr>
<td></td>
<td>- Tetracyclines</td>
</tr>
<tr>
<td></td>
<td>- Cotrimoxazole</td>
</tr>
<tr>
<td></td>
<td>- Chloramphenicol</td>
</tr>
<tr>
<td>Intracellular accumulation of MTX</td>
<td>- Dipyridamole</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>- Retinoids</td>
</tr>
<tr>
<td></td>
<td>- Ethanol</td>
</tr>
<tr>
<td></td>
<td>- Leflunomide</td>
</tr>
</tbody>
</table>

*Abbr.: MTX, methotrexate.*
More frequent laboratory monitoring is necessary when the dose is increased and in patients at increased risk of elevated MTX levels (dehydration, renal impairment, new drugs).

Chest X-ray: if there are symptoms such as acute fever, cough, dyspnea and cyanosis; Caution: MTX alveolitis

MTX in combination with folate is recommended to reduce toxicity. A common regimen consists of folate 5 mg the day after taking MTX.

Table 14 provides an overview of the laboratory tests recommended by the expert group for methotrexate therapy.

**Overdose/management of overdose**

See long version.

**Feasibility/special considerations/costs**

See long version.

### Secukinumab

<table>
<thead>
<tr>
<th>Treatment recommendations</th>
<th>Consensus strength</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab is recommended for induction therapy of moderate to severe psoriasis vulgaris, especially if other forms of therapy have failed, are not tolerated or are contraindicated.</td>
<td>↑↑ Strong consensus</td>
<td>Evidence- and consensus-based</td>
</tr>
</tbody>
</table>

### Secukinumab summary table

<table>
<thead>
<tr>
<th>Approval of secukinumab in Germany</th>
<th>2015 (moderate to severe psoriasis vulgaris and psoriatic arthritis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended initial dose</td>
<td>300 mg subcutaneously (2 injections of 150 mg) weekly in the first month, then 300 mg (2 injections of 150 mg) monthly</td>
</tr>
<tr>
<td>Recommended maintenance dose</td>
<td>300 mg subcutaneously monthly (2 injections of 150 mg)</td>
</tr>
</tbody>
</table>

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*Hb, Hct, erythrocytes, leukocytes, differential blood count, platelets.

**Annually, if weekly dose ≥ 15 mg.

***As indicated by patient history, clinical signs or other laboratory test results.

****May be considered before treatment and during follow-up in case of long-term treatment; further follow-up with FibroScan® if results are abnormal.

*****Abnormally low cell counts require weekly lab monitoring.

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Onset of clinical effect
PASI 75 response in 25% of patients after 3.5 weeks with 300 mg [6]

Selection of main contraindications
Active tuberculosis or other serious infectious disease

Selection of important ADRs
Candida infections

Selection of important drug interactions
Not known

Miscellaneous
IL-17A inhibitor

Dosage and dosing regimen
Secukinumab is administered by subcutaneous injection. For technical reasons, the required dose (300 mg) is divided into two doses of 150 mg (contained in two separate syringes), which are injected at the same time. The first five doses (each consisting of 2 injections of 150 mg) are given at weekly intervals, with subsequent treatment given monthly (2 injections of 150 mg).

Summary of the evidence
See long version.

Adverse drug reactions/safety
See long version and Summary of Product Characteristics.

Secukinumab can increase the risk of infection. In clinical studies, mild upper respiratory tract infections (nasopharyngitis, rhinitis) were observed slightly more often than in patients treated with placebo.

In clinical trials, patients treated with secukinumab more frequently developed Candida infections than individuals in the placebo group (roughly 3.5 cases per 100 treated patients per year, at a dose of 300 mg). The majority of such infections were cases of oral and vulvovaginal candidiasis. These were easily managed and did not require interruption of secukinumab therapy.

Main contraindications/limitations of use

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy and breast-feeding</td>
</tr>
<tr>
<td>Active tuberculosis or other serious infections</td>
</tr>
</tbody>
</table>

Important relative contraindications

- Crohn’s disease and ulcerative colitis (rare cases of exacerbation or initial manifestation of chronic inflammatory bowel disease were reported in clinical studies)
- Children and adolescents

Drug interactions

- Vaccination with live vaccines should be avoided during secukinumab therapy.
- There are no known classic drug interactions.

Notes on use

Depending on the clinical situation, fewer or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.

Pretreatment measures

- Rule out acute infection
- Tuberculosis must be definitively ruled out. See long version, section on “Tuberculosis”
- Ensure reliable contraception and rule out pregnancy in women of child-bearing age
- Patients should be informed that any infection may run an atypical and more severe clinical course and that they should seek medical attention as early as possible if an infection is suspected.

Measures during treatment

- Monitor for infection; if infection is suspected, treatment should be interrupted, at least temporarily.
- Suspicion of Candida infection requires diagnostic confirmation.

Posttreatment measures

- None

Table 15 provides an overview of the laboratory tests for secukinumab therapy recommended by the expert group.

Feasibility and costs

See long version.

Ustekinumab

<table>
<thead>
<tr>
<th>Treatment recommendations</th>
<th>Consensus strength</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab is recommended for induction therapy of moderate to severe psoriasis vulgaris, if other forms of therapy have failed, are not tolerated or are contraindicated.</td>
<td>↑↑ Strong consensus</td>
<td>Evidence- and consensus-based</td>
</tr>
</tbody>
</table>
Ustekinumab summary table

<table>
<thead>
<tr>
<th>Approval of ustekinumab in Germany</th>
<th>January 2009 (psoriasis vulgaris)</th>
<th>October 2013 (psoriatic arthritis)</th>
<th>June 2015 (psoriasis vulgaris in children and adolescents aged 12 and older)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended initial dose</td>
<td>45 mg (90 mg if &gt;100 kg body weight) at week 0 and 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended maintenance dose</td>
<td>45 mg (90 mg if &gt;100 kg body weight) every 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset of clinical effect</td>
<td>PASI 75 response in 25 % of patients after 4.6 weeks (90 mg) and 5.1 weeks (45 mg) [3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection of main contraindications</td>
<td>Active tuberculosis or other serious infectious diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection of important ADRs</td>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection of important drug interactions</td>
<td>Not known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>IL12/IL23p40 antagonist</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adverse drug reactions/safety

See long version and Summary of Product Characteristics.

In the placebo-controlled induction phases of the PHOENIX-1 and PHOENIX-2 trials, the rate of common and severe adverse drug reactions on ustekinumab was similar to that in the placebo groups. The most common adverse drug reactions were:

- Infections in general: 21.5 % and 31.4 %, respectively (placebo: 20 % and 26.7 %), including:
  - Nasopharyngitis: 6.8 % and 10.2 % (placebo: 7.1 % and 8.6 %)
  - Upper respiratory tract infections: 2.9 % and 7.1 % (placebo: 3.4 % and 6.3 %)
- Headache: 4.6 % and 5.5 % (placebo: 2.4 % and 4.1 %)
- Arthralgia: 2.4 % and 3.4 % (placebo: 2.7 % and 2.9 %)

The incidence of severe adverse events was 0.8 % and 2.0 %, respectively; these percentages were also observed in the placebo group (0.8 % and 2.0 %). Occasional severe adverse drug reactions in the PHOENIX-1 trial included two infections (bilateral erysipelas of the legs and herpes zoster); both were successfully managed with appropriate treatment. In the PHOENIX-2 trial, only one patient treated with ustekinumab developed a serious infection; here, too, the diagnosis was erysipelas.

The rate of severe infections remained low (< 1 %) in subsequent study phases. Taking both studies together, there were 15 malignancies throughout the observation period, including 11 cases of skin cancer. An integrated analysis of all safety data from phase II and III trials in psoriasis, which was presented to the US Food and Drug Administration (FDA), was based on data from 2,266 patients, of whom 70 % had received at least six months of ustekinumab treatment. This analysis showed no association with lymphopenia, nor were there any cumulative toxic effects. The
number of malignancies continued to be low and similar to the number in patients on placebo, thus corresponding to the expected incidence (based on epidemiological data) in healthy individuals. The same is true for serious cardiovascular events.

The duration of safety-relevant immunological effects cannot be inferred from the drug’s long duration of action and sustained clinical effect in between injections. Infections did not occur more frequently at the beginning of the injection interval, when drug levels are comparatively high, than at the end of the interval, when levels are low. For information on live vaccines, see below.

Based on data from studies of psoriatic arthritis as well as from treatment and pharmacovigilance registries, there is currently no evidence that the risk of developing cardiovascular events (MACE) is increased in psoriasis patients on ustekinumab, despite sometimes conflicting initial reports. The frequency of MACE in long-term studies is similar to that seen in long-term studies of TNF antagonists such as adalimumab.

Prevention/management of ADRs

Infections are among the most important adverse effects. Patients should therefore be informed about relevant early symptoms.

Although there have only been two published cases of tuberculosis in association with ustekinumab therapy [12, 13], patients should undergo tuberculosis screening as recommended in the section on “Tuberculosis” in the long version of this guideline. Active tuberculosis is a contraindication for using ustekinumab. Latent tuberculosis requires preventive measures during treatment.

Prior to administration of a live vaccine, ustekinumab therapy should be discontinued for at least 15 weeks and should be resumed no earlier than two weeks after the vaccination.

Table 16  Laboratory tests in patients on ustekinumab.

<table>
<thead>
<tr>
<th>Point in time → Diagnostic tests ↓</th>
<th>Before treatment</th>
<th>Week 4</th>
<th>Every 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>X</td>
<td>X</td>
<td>Before each injection</td>
</tr>
<tr>
<td>AST, ALT, GGT</td>
<td>X</td>
<td>X</td>
<td>Before each injection</td>
</tr>
<tr>
<td>Hepatitis B serology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV and hepatitis C serology*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test (urine)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If infection is suspected, see pretreatment measures

According to the Summary of Product Characteristics, no laboratory tests are currently suggested during treatment with ustekinumab. The guideline authors recommend the tests listed above. Depending on the clinical situation, fewer (for example every 6 months) or more measures or laboratory tests may be required. They should be selected for each patient on an individual basis.

*As indicated by patient history, clinical signs or other laboratory test results.
Measures during treatment
– Monitor for infection; if infection is suspected, treatment should be interrupted, at least temporarily.
– If the patient becomes pregnant, treatment should be interrupted if possible; if treatment is needed, see section on “Pregnancy”
– Treatment should be carried out by medically trained staff

Posttreatment measures
– None

Table 16 provides an overview of the laboratory tests for ustekinumab therapy recommended by the expert group.

Overdose/management of overdose
See long version.

Feasibility/special considerations/costs
See long version.

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References
8 Wyeth Information for Professionals. Current version.