Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

# Vorgang: 2019-B-045 Secukinumab (Plaque-Psoriasis bei Kindern)

Stand: Mai 2019

# I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

**Secukinumab**

[mittelschwere bis schwere Plaque-Psoriasis bei Kindern und Jugendlichen ab einem Alter von 6 Jahren]

| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
|---|---|
| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | *Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“* |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | Phototherapie: NB-UV-B-Bestrahlungen, Photosoletherapie |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung: Balneophototherapie vom 13. März 2008;<br>Richtlinie Methoden vertragsärztliche Versorgung, Stand: 3. Oktober 2014, des Gemeinsamen Bundesausschusses zu Untersuchungs- und Behandlungsmethoden der vertragsärztlichen Versorgung (Richtlinie Methoden vertragsärztliche Versorgung) in der Fassung vom 17. Januar 2006 veröffentlicht im Bundesanzeiger 2006 Nr. 48 (S. 1 523) in Kraft getreten am 1. April 2006; zuletzt geändert am 17. Juli 2014 veröffentlicht im Bundesanzeiger (BAnz AT 02.10.2014 B2); in Kraft getreten am 3. Oktober 2014.<br>15. Balneophototherapie<br><br>*Die Beschlüsse nach § 35a SGB V im vorliegenden Anwendungsgebiet beziehen sich ausschließlich auf erwachsene Patienten.*<br>Beschluss zu Apremilast vom 06.08.2015<br>Beschluss zu Secukinumab vom 27.11.2015<br>Beschluss zu Secukinumab vom 17.08.2017<br>Beschluss zu Ixekizumab vom 17.08.2017<br>Beschluss zu Brodalumab vom 01.03.2018<br>Beschluss zu Dimethylfumarat vom 16.03.2018<br>Beschluss zu Guselkumab vom 17.05.2018 |
| Die Vergleichstherapie soll nach dem allgemein anerkannten | *Siehe systematische Literaturrecherche* |

## I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

**Secukinumab**
[mittelschwere bis schwere Plaque-Psoriasis bei Kindern und Jugendlichen ab einem Alter von 6 Jahren]

**Kriterien gemäß 5. Kapitel § 6 VerfO**

| | |
|---|---|
| Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Secukinumab<br>L04AC10<br>Cosentyx® | „Zur Behandlung der mittelschweren bis schweren Plaque-Psoriasis bei Kindern und Jugendlichen ab einem Alter von 6 Jahren, die für eine Systemtherapie in Frage kommen.“ |
| **Systemische Therapie** | |
| Adalimumab<br>L04AB04<br>Humira® | Humira® ist indiziert zur Behandlung der mittelschweren bis schweren chronischen Plaque-Psoriasis bei erwachsenen Patienten, die Kandidaten für eine systemische Therapie sind.<br><br>*Plaque-Psoriasis bei Kindern und Jugendlichen*<br>Humira® ist indiziert zur Behandlung der schweren chronischen Plaque-Psoriasis bei Kindern und Jugendlichen ab dem Alter von 4 Jahren, die nur unzureichend auf eine topische Therapie und Phototherapien angesprochen haben oder für die diese Therapien nicht geeignet sind. |
| Etanercept<br>L04AB01<br>Enbrel® | Behandlung Erwachsener mit mittelschwerer bis schwerer Plaque-Psoriasis, die auf eine andere systemische Therapie wie Ciclosporin, Methotrexat oder Psoralen und UVA-Licht (PUVA) nicht angesprochen haben oder bei denen eine Kontraindikation oder Unverträglichkeit einer solchen Therapie vorliegt. |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| | *Plaque-Psoriasis bei Kindern und Jugendlichen*<br>Behandlung der chronischen schweren Plaque-Psoriasis bei Kindern und Jugendlichen ab dem Alter von 6 Jahren, die unzureichend auf eine andere systemische Therapie oder Lichttherapie angesprochen haben oder sie nicht vertragen. |
| Ustekinumab<br>L04AC05<br>Stelara® | Stelara® ist für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis indiziert, bei denen andere systemische Therapien einschließlich Ciclosporin, Methotrexat (MTX) oder PUVA (Psoralen und Ultraviolett A) nicht angesprochen haben, kontraindiziert sind oder nicht vertragen wurden.<br><br>*Plaque-Psoriasis bei Kindern und Jugendlichen*<br>Stelara® ist für die Behandlung der mittelschweren bis schweren Plaque-Psoriasis bei Kindern und Jugendlichen ab 12 Jahren indiziert, die unzureichend auf andere systemische Therapien oder Phototherapien angesprochen oder sie nicht vertragen haben. |
| Ciclosporin<br>L04AD01<br>Ciclosporin Pro 100 mg/ml Lösung | Behandlung von schwerer Psoriasis bei Patienten, bei denen eine herkömmliche Therapie nicht geeignet oder nicht wirksam ist.<br><br>*Anwendung bei Kindern in anderen Indikationen als Transplantationen*<br>Abgesehen von der Behandlung von nephrotischem Syndrom liegen keine entsprechenden Erfahrungen mit Ciclosporin bei Kindern vor. Eine Anwendung bei Kindern unter 16 Jahren außerhalb der Transplantationsindikationen mit Ausnahme des nephrotischen Syndroms kann daher nicht empfohlen werden. |
| ~~Dimethylfumarat, Ethylhydrogenfumarat~~<br>~~D05BX51~~<br>~~Fumaderm® initial~~<br>~~Fumaderm®~~ | ~~FUMADERM initial: Zur verträglichkeitsverbessernden Einleitung der FUMADERM-Therapie.~~<br>~~FUMADERM: Zur Behandlung von mittelschweren bis schweren Formen der Psoriasis vulgaris, sofern eine alleinige äußerliche Therapie nicht ausreichend ist. Eine vorhergehende Verträglichkeitsanpassung mit FUMADERM initial ist erforderlich.~~<br><br>~~Gegenanzeigen:~~<br>~~Fumaderm initial und Fumaderm sollen nicht angewendet werden:~~<br>~~- […]~~<br>~~- bei Personen unter 18 Jahren.~~ |
| Methotrexat<br>M01CX01<br>Lantarel®<br>Tabletten | Schwere Formen der Psoriasis vulgaris, insbesondere vom Plaque-Typ, und der Psoriasis arthropathica, die mit einer konventionellen Therapie nicht ausreichend behandelbar sind. |
| Acitretin<br>D05BB02<br>Neotigason® | Zur symptomatischen Behandlung von schwersten, einer konventionellen Therapie nicht zugänglichen Verhornungsstörungen des Hautorgans wie:<br>- Psoriasis vulgaris, vor allem erythrodermatische und pustulöse Formen |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| | |
|---|---|
| Kortikosteroide, z.B. Prednisolon H02AB06 Prednisolon-ratiopharm® Tabletten | […] Dermatologie:<br>Erkrankungen der Haut und Schleimhäute, die aufgrund ihres Schweregrades und/oder Ausdehnung bzw. Systembeteiligung nicht oder nicht ausreichend mit topischen Glucocorticoiden behandelt werden können. Dazu gehören: […]<br>- Erythemato-squamöse Dermatosen: z. B. Psoriasis pustulosa, Pityriasis rubra pilaris, Parapsoriasis-Gruppe (DS: c –a) […] (Stand: 08/2010) |

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

## Abteilung Fachberatung Medizin

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

## Vorgang: 2019-B-045 (Secukinumab)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 5. März 2019 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

| | |
|---|---|
| ADA | Antidrug antibodies |
| AE | Adverse event |
| AGREE | Appraisal of Guidelines Research and Evaluation |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| b.i.w. | Twice weekly |
| BB | broadband (Breitband) |
| CI | Konfidenzintervall |
| CoI | Conflict of interest |
| CSA | Ciclosporin |
| DAHTA | Deutsche Agentur für Health Technology Assessment |
| DLQI | Dermatology Life Quality Index |
| EADV | European Association for Dermatology and Venereology |
| EDF | European Dermatology Forum |
| EOW | Every other week |
| ETN | etanercept |
| G-BA | Gemeinsamer Bundesausschuss |
| GIN | Guidelines International Network |
| GoR | Grade of Recommendation |
| GRADE | Grading of Recommendations Assessment, Development, and Evaluation |
| IPC | International Psoriasis Council |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| k. A. | keine Angabe |
| LoE | Level of Evidence |
| MTC | mixed treatment comparisons |
| MTX | Methotrexate |
| NB | Narrowband (Schmalband) |
| NGC | National Guideline Clearinghouse |
| NICE | National Institute for Health and Care Excellence |
| PASI | Psoriasis Area and Severity Index |
| PGA | physician’s global assessment |
| PUVA | Psoralen plus UV-A (auch Photochemotherapie) |
| q.d. | Once daily |
| q.w. | Once weekly |
| SAE | Severe adverse event |
| SF-36 | Short-Form General Health Survey |

| | |
|---|---|
| SGB | Sozialgesetzbuch |
| SIGN | Scottish Intercollegiate Guidelines Network |
| TNF | Tumornekrosefaktor |
| TRIP | Turn Research into Practice Database |
| UV | ultraviolet |
| UVB | broad- or narrow-band |
| VAS | Visual analog scale |
| vs. | versus |
| WHO | World Health Organization |

# 1 Indikation

zur Behandlung der mittelschweren bis schweren chronischen Plaque-Psoriasis bei Kindern und Jugendlichen ab einem Alter von 6 Jahren, die für eine Systemtherapie in Frage kommen.

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Psoriasis* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 11.04.2017 durchgeführt, die Folgerecherchen am 20.02.2018 und am 21.12.2018. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherchen übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 1285 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 12 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen.

# 3 Ergebnisse

## 3.1 IQWiG Berichte/G-BA Beschlüsse

**G-BA, 2018 [8].**

Richtlinie des Gemeinsamen Bundesausschusses zu Untersuchungs- und Behandlungsmethoden der vertragsärztlichen Versorgung (Richtlinie Methoden vertragsärztliche Versorgung) in der Fassung vom 17. Januar 2006; veröffentlicht im Bundesanzeiger 2006 Nr. 48 (S. 1 523); in Kraft getreten am 1. April 2006; zuletzt geändert am 20. September 2018; veröffentlicht im Bundesanzeiger (BAnz AT 13.12.2018 B7); in Kraft getreten am 14. Dezember 2018

**Anwendungsgebiet**

(…) 15. Balneophototherapie

§ 1 Indikation

Die unter § 2 genannten Verfahren zur Balneophototherapie dürfen bei Patientinnen und Patienten mit mittelschwerer bis schwerer Psoriasis vulgaris zu Lasten der Gesetzlichen Krankenversicherung als vertragsärztliche Leistungen erbracht werden. Von einem mittelschweren bis schweren Verlauf wird in der Regel bei einem PASI-Score größer 10 ausgegangen. Für Patienten mit primär palmoplantarer Ausprägung gilt dieser Grenzwert bei der Bade-PUVA-Behandlung nicht.

§ 2 Anerkannte Verfahren

(1) Die Balneophototherapie kann als Photosoletherapie oder als Bade-PUVA erbracht werden.

(2) Für die Photosoletherapie stehen die synchrone und die asynchrone Anwendung zur Verfügung. Die synchrone Photosoletherapie besteht aus dem gleichzeitigen Bad in einer 10-prozentigen Tote-Meer-Salzlösung und einer Bestrahlung mit UV-B-Schmalbandspektrum (UV-B 311 nm) unter Verwendung von dafür nach Medizinprodukte-Betreiberverordnung (MPBetreibV) zugelassenen Behandlungssystemen. Bei der asynchronen Photosoletherapie erhält der Patient zuerst ein 20-minütiges Bad mit 25-prozentiger Kochsalzlösung und anschließend die Lichtbehandlung unter Anwendung von UV-Bestrahlungsgeräten mit Breitband-UV-B oder Schmalband-UV-B (311 nm) oder selektiver UV-B (SUP). Die asynchrone Photosoletherapie kann als Vollbad oder als Folienbad durchgeführt werden. Wird die asynchrone Photosoletherapie mit Hilfe einer Folie durchgeführt, liegt der Patient in einer mit warmen Leitungswasser gefüllten Badewanne, von einer Folie umhüllt, in die 4 bis 10 Liter einer 25-prozentigen Kochsalz-Lösung gegossen wurden. Die verwendete Folie muss für das Baden von Menschen in dieser Salzlösung geeignet sein.

(3) Die Bade-PUVA besteht aus einem Bad von 20 Minuten Dauer in einer lichtsensibilisierenden Lösung unter Verwendung einer für die Bade-PUVA arzneimittelrechtlich zugelassenen 8-Methoxypsoralen-Lösung mit nachfolgender UV-A-Bestrahlung; die hochdosierte selektive UV-A1-Bestrahlung ist hierbei nicht zu verwenden.

(4) Die Balneophototherapie darf nur in einer ärztlich geleiteten Betriebsstätte erfolgen. Eine nach dem Bad durchzuführende Lichtbehandlung muss unmittelbar im zeitlichen Anschluss an das Bad erfolgen.

§ 3 Häufigkeit und Anzahl der Anwendungen

(1) Bei allen Verfahren zur Balneophototherapie ist eine Behandlungshäufigkeit von 3 bis 5 Anwendungen pro Woche anzustreben. Die Behandlung ist auf höchstens 35 Einzelanwendungen beschränkt (Behandlungszyklus). Ein neuer Behandlungszyklus kann frühestens 6 Monate nach Abschluss eines vorangegangenen Behandlungszyklus erfolgen.

(2) Absatz 1 gilt auch, wenn während der Behandlung ein Wechsel der verschiedenen Formen der Balneophototherapie vorgenommen wird.

§ 4 Eckpunkte zur Qualitätssicherung

(1) Die Leistungen nach § 2 können nur von Fachärzten für Haut- und Geschlechtskrankheiten zu Lasten der Gesetzlichen Krankenversicherung erbracht und abgerechnet werden, die über Kenntnisse, Erfahrungen und Fertigkeiten mit der Lichtbehandlung verfügen.

(2) Im Rahmen der Behandlung sind vom Arzt zu gewährleisten:

- die Aufklärung der Patienten insbesondere auch über unerwünschte Wirkungen (z. B. Entwicklung von Malignomen) und Wechselwirkungen der Behandlung (z. B. Interaktion mit Medikamenten),

- die fachgerechte Durchführung der Bade- und Lichtbehandlung insbesondere im Hinblick auf die Handhabung und Einstellung der Behandlungsgeräte, die Umsetzung des anzuwendenden Behandlungsschemas sowie die Schulung des medizinischen Personals,

- die unmittelbare Erreichbarkeit des Arztes während der Behandlung, die fachgerechte, regelmäßige Wartung der Therapiegeräte inklusive der Kontrolle der Gerätedosimetrie,

- die Durchführung in geeigneten Räumlichkeiten.

§ 5 Dokumentation

Der behandelnde Arzt hat die Ausgangsbefunde (u. a. PASI-Wert) sowie den Behandlungsverlauf, die durchschnittliche Anzahl der Behandlungen pro Woche und Gesamtbehandlungsanzahl zu dokumentieren. Die Dokumentationen sind auf Verlangen den Kassenärztlichen Vereinigungen für Qualitätssicherungsmaßnahmen vorzulegen. (…)

## 3.2 Cochrane Reviews

**Sanclemente G et al., 2015 [12].**

Anti-TNF agents for paediatric psoriasis

**Fragestellung**

To assess the efficacy and safety of anti-TNF agents for the treatment of paediatric psoriasis.

**Methodik**

Population:

- any children (under 18 years old)with a clinical or histopathological diagnosis of chronic plaque psoriasis. This included types of psoriasis where there was an indication for the use of anti-TNF agents, that is children with moderate to severe plaque psoriasis who did not respond to, had a contraindication to, or who did not tolerate other systemic therapies, including ciclosporin, methotrexate, or photochemotherapy using psoralen (PUVA).

Intervention/Komparator:

- Any anti-TNF agent (or any agent that acts to block the biological activity of TNF-α at any dosage, administered either orally, subcutaneously, or intravenously, either alone or in combination with additional agents. The considered comparators were:
  - any alternative active treatment (PUVA, narrow-band ultraviolet B, acitretin, methotrexate, ciclosporin A, or any other biologic);
  - placebo; or
  - no treatment.

Endpunkte:

- Primär: PASI 75, quality of life, adverse outcomes
- Sekundär: Proportion of participants achieving PASI 50, PASI 90, or both; PGA; BSA; Patient Global Assessment; Psoriasis remission, recurrence, and resource use

Recherche/Suchzeitraum:

- up to July 2015

Qualitätsbewertung der Studien:

- Cochrane Apporach

**Ergebnisse**

Anzahl eingeschlossener Studien:

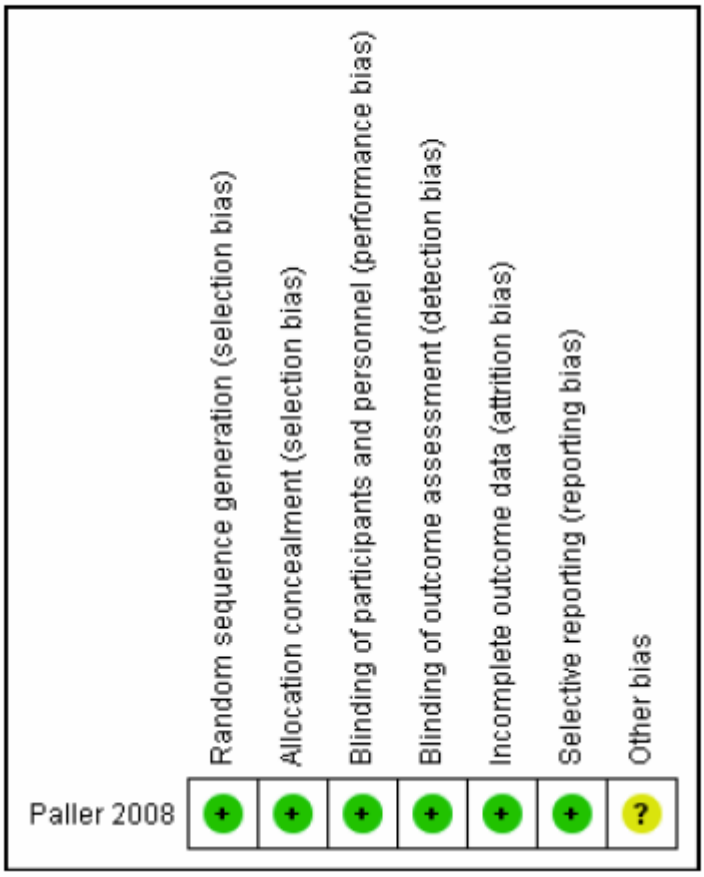
- We included one study with 211 participants (median age 13 years), in which etanercept (dosage ranged from0.8 to 50mg per kilogram of body weight) was compared to placebo. Follow-up was over a 48-week period.

Charakteristika der Population:

- paediatric psoriasis from 4 to 17 years of age, who must have had stable moderate to severe plaque psoriasis at screening. The median age of enrolled participants was 13 years, and 64% of participants were older than 11 years of age.
- They must also have had a poor response or a contraindication to previous or current treatment with phototherapy or systemic psoriasis therapy (for example, retinoids, methotrexate, or ciclosporin) or poorly controlled psoriasis with topical therapy.

Qualität der Studien:

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**




Studienergebnisse:

- At week 12, 57% versus 11% who received etanercept or placebo, respectively, achieved the PASI 75 (risk ratio 4.95, 95% confidence interval (CI) 2.83 to 8.65; high-quality evidence). Absolute risk reduction and the number needed to treat to obtain a benefit with etanercept was 45% (95% CI 33.95 to 56.40) and 2 (95% CI 1.77 to 2.95), respectively.
- The percentage improvement from baseline of the CDLQI scores at week 12 was better in the etanercept group than the placebo group (52.3%versus 17.5%, respectively (P = 0.0001)). Analysis between the groups showed an effect size that was clinically important (mean difference 2.30, 95% CI 0.85 to 3.75; high-quality evidence). However, means, medians, and minimal important difference results and results of the Pediatric Quality of Life

Inventory, Stein Impact on Family Scale, and Harter Self-Perception Profile for Children scores must be interpreted with caution, as they were not prespecified outcomes.

- Three serious adverse events were reported, but they were resolved without sequelae. Deaths or other events such as malignant tumours, opportunistic infections, tuberculosis, or demyelination were not reported in the included study.
- 13% of participants in the placebo group and 53% in the etanercept group had a PGA of clear or almost clear (risk ratio 3.96, 95% CI 2.36 to 6.66; high-quality evidence) at week 12.

**Anmerkung/Fazit der Autoren**

This review found only one RCT evaluating the use of this type of biological therapy. Although the risk of publication bias was high, as we included only one industry-sponsored RCT, the risk of allocation, selection, performance, attrition, and selective reporting biases for all outcomes (except for CDLQI) was low, and no short-term serious adverse events were found. We can conclude, based on this single included study, that etanercept seems to be efficacious and safe (at least in the short term) for the treatment of paediatric psoriasis. However, as the GRADE approach refers not to individual studies but to a body of evidence, we shall wait for the results of the ongoing studies in a future update of this review. In addition, future studies should evaluate quality-of-life endpoints established a priori and standardise primary outcome measures such as PASI 75, and should include the PGA as a secondary endpoint. Also, collating and reporting adverse events uniformly is required to better evaluate safety.

*Kommentare zum Review*

- As several trials of anti-TNF agents in paediatric psoriasis are ongoing, in future updates of this review we plan to perform metaanalyses if there are sufficient numbers of included studies.

## 3.3 Systematische Reviews

**Carrascosa JM et al., 2018 [2]**

Effects of etanercept on the patient-perceived results (PROs) in patients with moderate-to severe plaque psoriasis: systematic review of the literature and meta-analysis

**Fragestellung**

To evaluate the efficacy of etanercept (ETN) compared with placebo for moderate-to-severe psoriasis regarding patient-reported outcomes (PROs).

**Methodik**

Population:

- patients with moderate-to-severe plaque psoriasis

Intervention:

- etanercept (regardless oft he dose, administration intervals, duration of treatment, combination with other treatments)

Komparator:

- comparison group using placebo

Endpunkte:

- Clinical data of efficacy related to PROs, such quality of life, depression, anxiety, pruritus, and sleep, regardless of the questionnaire or system, such as a visual analog scale (VAS)

Recherche/Suchzeitraum:

- Medline, Embase, Cochrane Library to August 2017

Qualitätsbewertung der Studien:

- Jadad scale

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 12 studies

Charakteristika der Population:

- The RCT selected included patients with moderate-to-severe plaque psoriasis, most of them good or very good quality patients. About 80% of the patients were middle-aged males, biologically naïve, although several RCT included a small percentage of patients with previous biological agents. RCT duration ranged from 12 to 86 weeks (including open phases).
- Various RCT used ETN 50mg twice a week during the first 2 weeks and then continued with ETN 50 mg/week. Only those comparing ETN with placebo were selected.
- The most analyzed PRO was quality of life, especially using the Dermatology Life Quality Index (DLQI). Other PROs were the patients' global assessment of their disease, patients'

satisfaction with the treatment, their sleep habits, and variables related to their work environments, etc.

Qualität der Studien:

- For nine studies information about quality: 6 studies with a Jadad score of 3, 2 studies with a score of 5 and one studie with a score of 1.

Studienergebnisse:

- Compared with placebo, ETN significantly improved quality of life, patient global assessment, pruritus and pain in the short and medium term, fatigue in the short term (although the effect size and differences with placebo are unclear).
- ETN also produces a high patient's satisfaction, which increases over time and is higher compared with placebo and might improve depressive symptoms in the long term.

Table 1. Main results of the systematic literature review according to the PROs.

| PROs | Instrument/s | Main results | References |
|---|---|---|---|
| Quality of life | DLQI<br>EQ-5D<br>SF-36<br>Skindex-17 | ETN, compared with placebo, significantly improved quality of life in the short and medium term | (16,20,22–26,28,29,31–33) |
| PGA | Categorical scale (0–4)<br>Categorical scale (0–5)<br>VAS | ETN, compared with placebo, significantly PGA of life in the short and medium term | (23) |
| Pruritus | Generic numeric scale<br>Specific numeric scale<br>ISI<br>VAS | ETN, compared with placebo, significantly improved pruritus in the short and medium term | (16,29) |
| Fatigue | FACIT-F | ETN might improve fatigue in the short term, but the effect size and differences with placebo Are unclear | (26,27) |
| Satisfaction | Categorical scale<br>TMSQ<br>VAS | ETN produces a high patients satisfaction, which increases over time and is higher compared with placebo | (21,29) |
| Depression, depressive symptoms | HADS<br>BDI<br>PROMIS emotional distress/depression score<br>Ham-D | ETN might improve depressive symptoms also in the long term | (27,29) |
| Pain | VAS<br>Generic numeric scale<br>SF-36 pain subscale | ETN, significantly improved the pain in the short and medium term more than placebo | (29) |

PROs: Patient-reported outcomes; DLQI: Dermatology Life Quality Index; EQ-5D: Euroqol 5 dimensions; SF-36: Short Form 36 items; ETN: etanercept; PGA: patients global assessment; VAS: visual analog scale; ISI: Itch Severity Item; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; TSQM: Treatment Satisfaction Questionnaire for Medication; HADS: Hospital Anxiety and Depression Scale; BDI: Beck Depression Inventory; Ham-D: Hamilton Rating Scale for Depression.

**Anmerkung/Fazit der Autoren**

To sum up, this systematic review has revealed ETN efficacy in relation to PROs of patients with moderate-to-severe plaque psoriasis.

The assessment of ETN and other biological drugs impacts on PROs allows for a holistic view of this therapeutic strategy, useful both for healthcare professionals and for other elements of the circuit which are involved in decision-making.

*Hinweise zum Review:*

- About 80% of the patients were middle-aged males.

## 3.4 Leitlinien

**Nast A et al., 2017 [10].**

S3-Leitlinie zur Therapie der Psoriasis vulgaris, Update 2017

Siehe auch Nast A et al., 2017 [9] & Gaskins M et al., 2018 [7]

**Leitlinienorganisation/Fragestellung**

Allgemeines Ziel der Leitlinie ist es, Ärzten in der Praxis und Klinik eine akzeptierte, evidenzbasierte Entscheidungshilfe für die Auswahl sowie Durchführung einer geeigneten und suffizienten Therapie für Patientinnen und Patienten mit Psoriasis vulgaris zur Verfügung zu stellen. Dabei bezieht sich die Leitlinie auf die Induktionstherapie der leichten bis schweren Psoriasis vulgaris der männlichen und weiblichen Erwachsenen.

**Methodik**

Grundlage der Leitlinie:

Bei der Darstellung der Therapien wurde eine bewusste Beschränkung auf die aus der Sicht der Experten der Leitliniengruppe besonders relevanten Aspekte vorgenommen. Aspekte, die nicht speziell für eine bestimmte Intervention von Bedeutung sind, sondern der allgemeinen ärztlichen Sorgfaltspflicht entsprechen, wie das Prüfen von Unverträglichkeiten und Allergien gegenüber bestimmten Arzneimitteln, der Ausschluss von Gegenanzeigen u. a., wurden nicht einzeln aufgeführt, sondern als Teil der ärztlichen Sorgfaltspflicht vorausgesetzt.

Die aktuelle Fassung hat eine Gültigkeit bis zum 31 Dezember 2020.

Recherche/Suchzeitraum:

- Bis 2016
- Die aktuelle Fassung hat eine Gültigkeit bis zum 31. Dezember 2020.

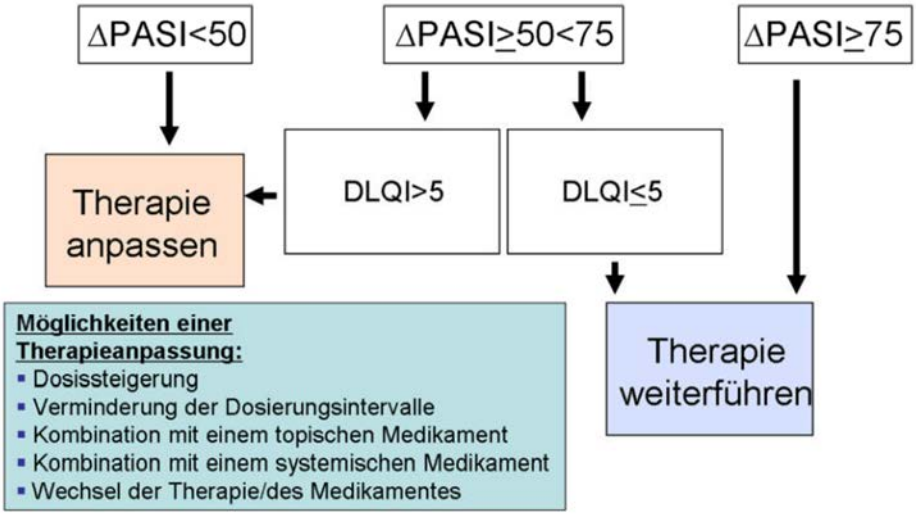
LoE und GoR:

- Die im Text formulierten Empfehlungen werden bei ausgewählten Schlüsselempfehlungen grafisch durch die Darstellung der Stärke der Therapieempfehlung unterstützt. Zur Vereinheitlichung und Standardisierung der Empfehlungen wurden folgende Standardformulierungen verwendet:
- ↑↑ wird empfohlen (starke Empfehlung für eine Maßnahme)
- ↑ kann empfohlen werden (Empfehlung für eine Maßnahme)
- → kann erwogen werden (offene Empfehlung)
- ↓ kann nicht empfohlen werden (Empfehlung gegen eine Maßnahme)

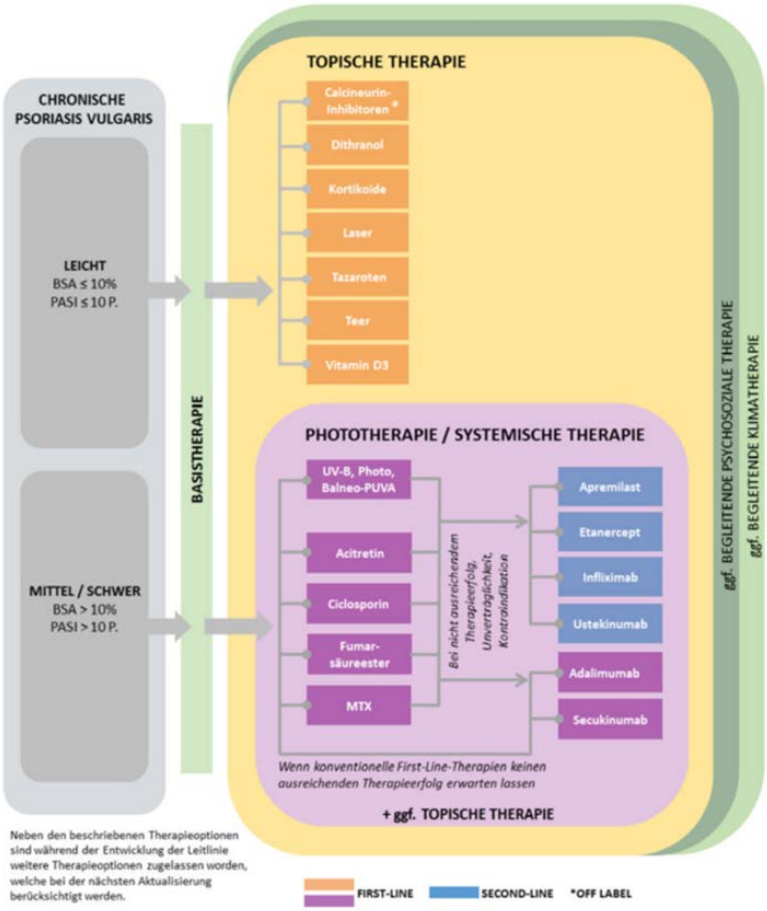
**Empfehlungen**

Ein klares Stufenverfahren der Therapieoptionen oder ein strikter klinischer Algorithmus können für die Behandlung der Psoriasis vulgaris derzeit nicht erstellt werden. Die Kriterien zur Auswahl der Therapie sind vielschichtig. Ein individuelles Abwägen und Gewichten einzelner für die Therapieauswahl relevanter Aspekte muss immer vorgenommen werden. Die Entscheidung für oder gegen eine Therapie bleibt eine Einzelfallentscheidung.

Therapieziele der der Behandlung von Psoriasis:




Therapieoptionen: Übersicht der beurteilten Therapieoptionen bei der chronischen Psoriasis vulgaris (die Anordnung der Therapieoptionen ist alphabetisch und stellt keineWertung dar)



Tabellarische Bewertung zur Einschätzung der systemischen Therapieoptionen:

| Wirkstoff | Wirk-samkeit[1] | Qualität der Evidenz nach Grade PASI 75 vs. Placebo | Sicherheit / Verträglichkeit bei Induktions-therapie* | Sicherheit / Verträglichkeit bei Erhaltungs-therapie* | Praktikabilität (Patient)* | Praktikabilität (Arzt)* |
|---|---|---|---|---|---|---|
| Acitretin** | 0/+* | Kein Vergleich verfügbar | + | + | + | ++ |
| Adalimumab | +++* | ⊕⊕⊕◯ | ++ | ++ | +++ | ++ |
| Apremilast | + | ⊕⊕⊕◯ | ++ | ++ | +++ | +++ |
| Ciclosporin | +* | ⊕⊕◯◯ | + | + | +++ | ++ |
| Etanercept | ++* | ⊕⊕⊕⊕ | ++ | ++ | +++ | ++ |
| Fumarate | +* | ⊕⊕◯◯ | + | ++ | ++ | ++ |
| Infliximab | ++++ | ⊕⊕◯◯ | + | ++ | +++ | +/- |
| Methotrexat | + | ⊕⊕◯◯ | + | ++ | +++ | ++ |
| Secukinumab | ++++ | ⊕⊕⊕⊕ | ++ | ++ | +++ | ++ |
| Ustekinumab | +++ | ⊕⊕⊕◯ | ++ | ++ | ++++ | +++ |

[1] 1 - bis ++++ - Einschätzung derWirksamkeit unter Berücksichtigung von PASI 75 Ergebnissen
[2] (Placebo und Head-to-Head Studien) sowie Experteneinschätzung
[3] * Unter Berücksichtigung von Experteneinschätzung
** Für Frauen im gebärfähigen Alter wird eine Therapie mit Acitretin generell nicht empfohlen

### Systemische Therapien

- Acitretin

| Therapieempfehlungen | | Konsens-stärke | Kommentar |
|---|---|---|---|
| Acitretin kann zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris erwogen werden. | → | Konsens | Evidenz- und konsensusbasiert |
| Acitretin kann bei gebärfähigen Frauen mit Psoriasis vulgaris nicht empfohlen werden. | ↓ | Starker Konsens | Klinischer Konsensuspunkt |

- Adalimumab

| Therapieempfehlungen | | Konsens-stärke | Kommentar |
|---|---|---|---|
| Adalimumab wird zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen, vor allem wenn andere Therapieformen keinen ausreichenden Therapieerfolg erwarten lassen, gezeigt haben, unverträglich oder kontraindiziert sind. | ↑↑ | Starker Konsens | Evidenz- und konsensusbasiert |

- Apremilast

| Therapieempfehlungen | | Konsens-stärke | Kommentar |
|---|---|---|---|
| Apremilast kann zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen werden, wenn andere Therapieformen keinen ausreichenden Therapieerfolg gezeigt haben, unverträglich oder kontraindiziert sind. | ↑ | Starker Konsens | Evidenz- und konsensusbasiert |

- Ciclosporin

| Therapieempfehlungen | | Konsens-stärke | Kommentar |
|---|---|---|---|
| Ciclosporin kann zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen werden. | ↑ | Starker Konsens | Evidenz- und konsensusbasiert |
| Eine Kombination von Ciclosporin mit topischen Präparaten zur Behandlung bei mittelschwerer bis schwerer Psoriasis vulgaris kann empfohlen werden. | ↑ | Starker Konsens | Evidenz- und konsensusbasiert |

- Etanercept

| Therapieempfehlungen | | Konsens-stärke | Kommentar |
|---|---|---|---|
| Etanercept kann in der Dosierung von 1 x 50 mg zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen werden, wenn andere Therapieformen keinen ausreichenden Therapieerfolg gezeigt haben, unverträglich oder kontraindiziert sind. | ↑ | Konsens | Evidenz- und konsensusbasiert |

- Fumarsäureester

| Therapieempfehlungen | | Konsens-stärke | Kommentar |
|---|---|---|---|
| Die Behandlung mit Fumarsäureestern kann als Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen werden. | ↑ | Starker Konsens | Evidenz- und konsensusbasiert |

- Infliximab

| Therapieempfehlungen | | Konsens-stärke | Kommentar |
|---|---|---|---|
| Infliximab wird zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen, wenn andere Therapieformen keinen ausreichenden Therapieerfolg gezeigt haben, unverträglich oder kontraindiziert sind. | ↑↑ | Mehrheit-liche Zu-stimmung | Evidenz- und konsensusbasiert |

- Methotrexat

| Therapieempfehlungen | | Konsens-stärke | Kommentar |
|---|---|---|---|
| MTX kann zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen werden. | ↑ | Starker Konsens | Evidenz- und konsensusbasiert |

- Secukinumab

| Therapieempfehlungen | | Konsens-stärke | Kommentar |
|---|---|---|---|
| Secukinumab wird zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen, vor allem wenn andere Therapieformen keinen ausreichenden Therapieerfolg erwarten lassen, gezeigt haben, unverträglich oder kontraindiziert sind. | ↑↑ | Starker Konsens | Evidenz- und konsensusbasiert |

- Ustekinumab

| Therapieempfehlungen | | Konsens-stärke | Kommentar |
|---|---|---|---|
| Ustekinumab wird zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen, wenn andere Therapieformen keinen ausreichenden Therapieerfolg gezeigt haben, unverträglich oder kontraindiziert sind. | ↑↑ | Starker Konsens | Evidenz- und konsensusbasiert |

**Phototherapie**

| Therapieempfehlung | |
|---|---|
| UV-B und PUVA werden zur Induktionstherapie bei mittelschwerer und schwerer Psoriasis vulgaris vor allem bei großflächiger Erkrankung empfohlen. | ↑↑ |
| Trotz der besseren Wirksamkeit von PUVA im Vergleich zur reinen UV-B-Therapie kann auf Grund der besseren Praktikabilität und auf Grund des geringern Malignitätsrisikos eine Schmalspektrum UV-B-Therapie als Phototherapie der ersten Wahl empfohlen werden. | ↑ |
| Der Einsatz des Excimer Lasers kann für die gezielte Behandlung einzelner psoriatischer Plaques empfohlen werden. | ↑ |
| Eine Kombination mit topischem Vitamin $D_3$-Derivaten kann zur Verbesserung der Ansprechrate empfohlen werden. | ↑ |
| Die übliche Kombination mit Dithranol und Kortikoiden kann nur auf Grund klinischer Erfahrung empfohlen werden, nicht aber aufgrund der Datenlage. | ↑ |
| Wegen der geringen Praktikabilität und der Assoziation langfristiger unerwünschter Wirkungen mit der kumulativen UV-Dosis kann die Phototherapie nicht für Langzeitbehandlungen empfohlen werden. | ↓ |

Hintergrund: Bezüglich einer Monotherapie erfüllen 35 Studien zur UV-Phototherapie, 40 Studien zur PUVA Therapie sowie neun Studien zu Therapieverfahren mittels Laser die Einschlusskriterien der Leitlinie. Etwa 50 - 75 % aller mit UV-B-Phototherapien behandelten Patienten erreichen eine mindestens 75 %ige Verbesserung des PASI nach vier bis sechs Wochen, häufig wird eine vollständige Erscheinungsfreiheit erzielt (EN 2). Etwa 75 - 100 % aller mit PUVA-Therapie behandelten Patienten erreichen eine mindestens 75 %ige Verbesserung des PASI nach vier bis sechs Wochen, häufig wird eine vollständige Erscheinungsfreiheit erzielt (EN 2). Unter den unerwünschten Wirkungen steht die Dermatitis solaris durch Überdosierung weit im Vordergrund und wird häufig beobachtet. Bei wiederholter oder längerfristiger Anwendung müssen die Folgen hoher kumulativer UV-Dosen bedacht werden wie beispielsweise vorzeitige Hautalterung. Daneben besteht ein kanzerogenes Risiko, das bei oraler PUVA gesichert, für lokale PUVA und UV-B wahrscheinlich ist.

Die Praktikabilität der Therapie wird durch die Bindung räumlicher, finanzieller und personeller / zeitlicher Ressourcen auf ärztlicher Seite sowie durch den hohen zeitlichen Aufwand für den Patienten deutlich eingeschränkt. Für die Phototherapie resultiert ein gutes Kosten-Nutzen-Verhältnis aus der Perspektive der Kostenträger. Zu beachten ist jedoch der möglicherweise erhebliche Kosten- und Zeitaufwand für den Patienten.

**Topische Therapie**

- Calcineurin-Inhibitoren

| Therapieempfehlung | |
|---|---|
| Tacrolimus und Pimecrolimus topisch angewendet 1 - 2 x/d können zur Behandlung der Psoriasis vulgaris bei besonderen Lokalisationen der Psoriasisläsionen, wie Gesicht, Intertrigines und Genito-Anal-Bereich, erwogen werden. | → |
| Eine Anwendung am übrigen Körper kann aufgrund der nicht ausreichenden Datenlage bei vorhandenen Therapiealternativen sowie aufgrund der fehlenden Zulassung nicht empfohlen werden. | ↓ |

- Glukokortikosteroide

| Therapieempfehlung | |
|---|---|
| Eine Induktionstherapie mit topischen Kortikoiden der Wirkstoffklasse III wird bei leichter bis mittelschwerer Psoriasis vulgaris empfohlen. | ↑↑ |
| Eine Induktionstherapie mit topischen Kortikoiden der Wirkstoffklasse IV kann unter Abwägung von erhöhter Wirksamkeit und theoretisch erhöhtem Risiko unerwünschter Arzneimittelwirkungen bei leichter bis mittelschwerer Psoriasis vulgaris empfohlen werden. | ↑ |

*Hiweis zur Leitlinie:*

- Keine gesonderten Empfehlungen für Kinder/Jugendliche

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**Armstrong AW et al., 2015 [1].**

Combining biologic therapies with other systemic treatments in psoriasis: evidence-based, best-practice recommendations from the Medical Board of the National Psoriasis Foundation

**Leitlinienorganisation/Fragestellung**

"To make evidence-based, best-practice recommendations regarding combining biologics with other systemic treatments, including phototherapy, oral medications, or other biologics, for psoriasis treatment."

**Methodik**

Grundlage der Leitlinie:

Grading Skala in Anlehnung an Robinson et al.: Systematic reviews: grading recommendations and evidence quality. Arch Dermatol. 2008; 144(1):97-99.

Recherche/Suchzeitraum:

- 1/01/1946 bis 18/06/2013 in MEDLINE

LoE/GoR:

Table 1. Grading for Recommendation and Evidence[a]

| Strength of Recommendation | Grading for Recommendation | Level of Evidence | Quality of Supporting Evidence |
|---|---|---|---|
| 1 | Strong recommendation; high-quality, patient-oriented evidence | A | Systematic review or meta-analysis, randomized clinical trials with consistent findings, all-or-none observational study |
| 2A | Weak recommendation; limited-quality, patient-oriented evidence | B | Systematic review or meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings, lower-quality clinical trial, cohort study, case-control study |
| 2B | Weak recommendation, low-quality evidence | C | Consensus guidelines, usual practice, expert opinion, case series |

[a] The grading scale was adapted from the study by Robinson et al.[16]

**CoI**: Dr Armstrong reported serving as an investigator for or consultant to AbbVie, Lilly, Janssen, Amgen, Merck, and Pfizer. Dr Bagel reported serving as a consultant, speaker, and investigator for Amgen and AbbVie. Dr Van Voorhees reported serving as an advisor for Amgen, AbbVie, Janssen, LEO Pharma, and Warner Chilcott. She reported receiving grants from Amgen and AbbVie. She reported serving as a consultant for Amgen and as a speaker for Amgen, AbbVie, and Janssen. Dr Robertson reported being employed by the National Psoriasis Foundation, which receives unrestricted financial support from companies that make products used to treat psoriasis and psoriatic arthritis, including AbbVie, Amgen, Celgene Corporation, Lilly, Galderma Laboratories, Janssen, LEO Pharma, Novartis, Pfizer Inc, and Stiefel, a GSK company. No other disclosures were reported.

**Empfehlungen**

Table 2. Strength of Recommendations for the Use of Biologics in Combination With Phototherapy for Psoriasis Treatment

| Agent | Strength of Recommendation | Level of Evidence | Source |
|---|---|---|---|
| Etanercept and phototherapy | 2A | B | Kircik et al,[21] 2008; Gambichler et al,[17] 2011; Park et al,[18] 2013; De Simone et al,[22] 2011; Wolf et al,[23] 2009; Lynde et al,[24] 2012 |
| Adalimumab and phototherapy | 2A | B | Bagel,[25] 2011; Wolf et al,[19] 2011 |
| Ustekinumab and phototherapy | 2B | C | Wolf et al,[20] 2012 |

*Evidenzbasis*

[17] Gambichler T et al. Etanercept plus narrowband ultraviolet B phototherapy of psoriasis is more effective than etanercept monotherapy at 6 weeks. *Br J Dermatol*. 2011;164(6):1383-1386.

[18] Park KK et al. A randomized, "head-to-head" pilot study comparing the effects of etanercept monotherapy vs. etanercept and narrowband ultraviolet B (NB-UVB) phototherapy in obese psoriasis patients. *J Eur Acad Dermatol Venereol*. 2013; 27(7):899-906.

[19] Wolf P et al. 311 nm Ultraviolet B–accelerated response of psoriatic lesions in adalimumab-treated patients. *Photodermatol Photoimmunol Photomed*. 2011;27(4):186-189.

[20] Wolf P et al. Treatment with 311-nm ultraviolet B enhanced response of psoriatic lesions in ustekinumab-treated patients: a randomized intraindividual trial. *Br J Dermatol*. 2012;166(1):147-153.

[21] Kircik L et al. UNITE Study Group. Utilization of Narrow-band Ultraviolet Light B Therapy and Etanercept for the Treatment of Psoriasis (UNITE): efficacy, safety, and patient-reported outcomes. *J Drugs Dermatol*. 2008;7(3):245-253.

[22] De Simone C et al. Combined treatment with etanercept 50mg once weekly and narrow-band ultraviolet B phototherapy in chronic plaque psoriasis. *Eur J Dermatol*. 2011;21(4):568-572.
[23] Wolf P et al. Treatment with 311-nm ultraviolet B accelerates and improves the clearance of psoriatic lesions in patients treated with etanercept. *Br J Dermatol*. 2009;160(1):186-189.
[24] Lynde CW et al. A randomized study comparing the combination of nbUVB and etanercept to etanercept monotherapy in patients with psoriasis who do not exhibit an excellent response after 12 weeks of etanercept. *J Dermatolog Treat*. 2012;23(4):261-267.
[25] Bagel J. Adalimumab plus narrowband ultraviolet B light phototherapy for the treatment of moderate to severe psoriasis. *J Drugs Dermatol*. 2011;10(4):366-371.

**Table 3. Strength of Recommendations for the Use of Biologics in Combination With Traditional Oral Systemic Medications for Psoriasis Treatment**

| Agent | Strength of Recommendation | Level of Evidence | Source |
|---|---|---|---|
| **Biologics and Methotrexate in Combination Therapy** | | | |
| Etanercept and methotrexate | 1 | A | Zachariae et al,[26] 2008; Gottlieb et al,[27] 2012; Driessen et al,[29] 2008 |
| Infliximab and methotrexate | 2A | B | Dalaker and Bonesrønning,[28] 2009; Goedkoop et al,[30] 2004; Kavanaugh et al,[31] 2007 |
| Adalimumab and methotrexate | 2B | C | De Groot et al,[32] 2008 |
| **Biologics and Acitretin in Combination Therapy** | | | |
| Etanercept and acitretin | 2A, etanercept plus acitretin similar efficacy to etanercept alone | B | Gisondi et al,[34] 2008; Smith et al,[35] 2008 |
| Infliximab and acitretin | 2B, favors combination | C | Smith et al,[35] 2008 |
| Adalimumab and acitretin | 2B, favors combination | C | Smith et al,[35] 2008 |
| **Biologics and Cyclosporine in Combination Therapy** | | | |
| Etanercept and cyclosporine | 2B | C | Yamauchi and Lowe,[36] 2006; Lee et al,[37] 2010 |
| Adalimumab and cyclosporine | 2B | C | Gattu et al,[38] 2009 |

<u>*Evidenzbasis*</u>

*26 Zachariae Cet al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect ofmethotrexate therapy. Acta Derm Venereol. 2008;88(5):495-501.*
*27 Gottlieb AB et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. Br J Dermatol. 2012;167(3):649-657.*
*28 Dalaker M, Bonesrønning JH. Long-term maintenance treatment of moderate-to-severe plaque psoriasis with infliximab in combination with*
*methotrexate or azathioprine in a retrospective cohort. J Eur Acad Dermatol Venereol. 2009;23(3): 277-282.*
*29 Driessen RJ et al. Etanercept combined with methotrexate for high-need psoriasis. Br J Dermatol. 2008;159(2): 460-463.*
*30 Goedkoop AY et al. Deactivation of endothelium and reduction in angiogenesis in psoriatic skin and synovium by low dose infliximab therapy in combination with stable methotrexate therapy: a prospective single-centre study. Arthritis Res Ther. 2004;6(4):R326-R334.*
*31 Kavanaugh et al. IMPACT 2 Study Group. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. Ann Rheum Dis. 2007;66(4):498-505.*
*32 De Groot M et al. Adalimumab in combination with methotrexate more effectively reduces the numbers of different inflammatory cell types in lesional psoriatic skin than does single treatment with adalimumab or methotrexate. Br J Dermatol. 2008;158(6):1401.*

*34 Gisondi P et al. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol. 2008;158(6):1345-1349.*
*35 Smith EC et al. Combining systemic retinoids with biologic agents for moderate to severe psoriasis. Int J Dermatol. 2008;47(5):514-518.*
*36 Yamauchi PS et al. Cessation of cyclosporine therapy by treatment with etanercept in patients with severe psoriasis. J AmAcad Dermatol. 2006;54(3) (suppl 2):S135-S138.*
*37 Lee EJ et al. A clinical trial of combination therapy with etanercept and low dose cyclosporine for the treatment of refractory psoriasis. Ann Dermatol. 2010;22(2): 138-142.*
*38 Gattu S et al. Can adalimumab make a smooth and easy transition from cyclosporine a reality? a case series of successful transitions. Psoriasis Forum. 2009;15(2):33-35.*

**Table 4. Strength of Recommendations for the Use of a Biologic in Combination With Another Biologic for Psoriasis Treatment**

| Agent | Strength of Recommendation | Level of Evidence | Source |
|---|---|---|---|
| Etanercept and ustekinumab | 2B | C | Cuchacovich et al,[48] 2012; Heinecke et al,[49] 2013 |
| Etanercept and alefacept | 2B | C | Krell,[50] 2006 |
| Etanercept and efalizumab | 2B | C | Hamilton,[45] 2008; Adişen et al,[46] 2008; Kitamura et al,[47] 2009 |
| Adalimumab and ustekinumab | 2B | C | Heinecke et al,[49] 2013 |
| Infliximab and efalizumab | 2B | C | Lowes et al,[44] 2005; Hamilton,[45] 2008 |

*Evidenzbasis*
*44 LowesMA et al. Psoriasis vulgaris flare during efalizumab therapy does not preclude future use: a case series. BMC Dermatol. 2005;5:9.*
*45 Hamilton TK. Treatment of psoriatic arthritis and recalcitrant skin disease with combination therapy. J Drugs Dermatol. 2008;7(11):1089-1093.*
*46 Adişen E et al. When there is no single best biological agent: psoriasis and psoriatic arthritis in the same patient responding to two different biological agents. Clin Exp Dermatol. 2008;33(2):164-166.*
*47 Kitamura G et al. A case of tuberculosis in a patient on efalizumab and etanercept for treatment of refractory palmopustular psoriasis and psoriatic arthritis. Dermatol Online J. 2009;15(2):11.*
*48 Cuchacovich R et al. Combination biologic treatment of refractory psoriasis and psoriatic arthritis. J Rheumatol. 2012; 39(1):187-193.*
*49 Heinecke GM et al. Combination use of ustekinumab with other systemic therapies: a retrospective study in a tertiary referral center. J Drugs Dermatol. 2013;12 (10):1098-1102.*
*50 Krell JM. Use of alefacept and etanercept in 3 patients whose psoriasis failed to respond to etanercept. J AmAcad Dermatol. 2006;54(6): 1099-1101. Clinical Review & Education Review Biologic Therapies and Other Psoriasis Treatments 438*

*Hiweis zur Leitlinie:*

- Keine gesonderten Empfehlungen für Kinder/Jugendliche

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**European Dermatology Forum (EDF), 2016 [5] & 2017 [4].**

Siehe auch: & Dressler C et al., 2017 [3]

*EDF in cooperation with EADV and IPC*

European S3-Guidelines on the systematic treatment of psoriasis vulgaris.

**Leitlinienorganisation/Fragestellung**

The primary goal of these guidelines was to assist health care professionals in the choice of the optimal systemic treatment for their psoriasis patients with the specific circumstances of the individual patient.

**Methodik**

Grundlage der Leitlinie:

These guidelines are an update of the existing European Psoriasis Guidelines published in 2009. The guidelines have a validity until 31.12.2019. However, an update with respect to new medications will be added before that date.

Recherche/Suchzeitraum:

- systematische Recherche in Cochrane Library, Medline, Medline In-Process und Embase
- Update 2015 und 2017: An update of the European S3-Guidelines on the systemic treatment of psoriasis vulgaris – the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV) and the International Psoriasis Council (IPC – was published in December 2015 1, 2. In addition to the interventions discussed in the update, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) approved apremilast and secukinumab as new treatment options for psoriasis.

LoE/GoR:

- evidence and consensus-based guidelines: Erstellung nach AGREE II
- “All recommendations were consented using formal consensus methodologies (Delphi process and nominal group technique).”
- Bewertung über GRADE / GoR (siehe Anhang Tabelle 1)
- Level of consensus: ‚strong consensus‘ = agreement of > 90 % of the members of the expert group; ‘consensus’ = 75 to 89 % agreement; ‘weak consensus’ = 50 to 74 % agreement.

Sonstige methodische Hinweise

- Für die Themenbereiche ‘Special considerations and special patient populations’ wurden die Empfehlungen auf Basis von Expertenmeinung generiert. Keine systematische Bewertung.
- “The guidelines project has kindly been supported by the EDF. The financial support did not influence the guidelines development.”
- CoI aller Mitarbeitenden
- Outcome-Erfassung 16 Wochen nach Therapiebeginn, Ausschluss falls nur Outcome vor der 8. Woche nach Therapiebeginn vorlag. Für long-term therapy: Ergebnisse ab der 24. Woche nach Therapiebeginn.

**Empfehlungen**

Apremilast

| Recommendation | | Strength of consensus | Comment |
|---|---|---|---|
| We suggest apremilast as second-line medication for the induction and long-term treatment. | ↑ | Strong consensus | Evidence- and consensus-based |

**Therapeutic combinations**

| Recommendation | | Strength of consensus | Comments |
|---|---|---|---|
| Acitretin | o | Strong consensus | No evidence available |
| Adalimumab | o | Strong consensus | No evidence available |
| Ciclosporin | o | Strong consensus | No evidence available |
| Etanercept | o | Strong consensus | No evidence available |
| Fumaric acid esters | o | Strong consensus | No evidence available |
| Infliximab | o | Strong consensus | No evidence available |
| Methotrexate | o | Strong consensus | No evidence available of the clinical benefit of this association in patients with chronic plaque psoriasis. A single pharmacokinetic study showed that methotrexate and apremilast can be co-administered without any effect on the pharmacokinetic exposure of either agent. |
| Secukinumab | o | Strong consensus | No evidence available |
| Ustekinumab | o | Strong consensus | No evidence available |

Secukinumab

| Recommendation | | Strength of consensus | Comment |
|---|---|---|---|
| We recommend secukinumab for the induction and long-term treatment.<br><br>The use as first or second-line* medication should be done taking individual factors and regional regulations into account.<br><br>* if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated | ↑↑ | Consensus<br><br>Consensus | Evidence- and consensus-based |

| Recommendation | | Strength of consensus | Comments |
|---|---|---|---|
| Acitretin | o | Strong consensus | No evidence available |
| Adalimumab | ↓ | Strong consensus | Expert opinion:<br>increased risk of immunosuppression |
| Apremilast | o | Strong consensus | No evidence available |
| Ciclosporin | o | Strong consensus | No evidence available |
| Etanercept | ↓ | Strong consensus | Expert opinion:<br>increased risk of immunosuppression |
| Fumaric acid esters | o | Strong consensus | No evidence available |
| Infliximab | ↓ | Strong consensus | Expert opinion:<br>increased risk of immunosuppression |
| Methotrexate | ↑ | Strong consensus | Expert opinion:<br>Combination used in rheumatology [22] |
| Ustekinumab | ↓ | Strong consensus | Expert opinion:<br>increased risk of immunosuppression |

Acitretin

| **Recommendation** | | Strength of consensus | Comment |
|---|---|---|---|
| Based on the available evidence we cannot make a recommendation for or against the use of acitretin as a mono-therapy. | o | Consensus | Evidence and consensus based |
| Based on clinical experience and depending on the most important outcome for the individual patient, we suggest a low dose (20 to 30 mg daily) with respect to tolerability and a high dose (> 30 mg daily) with respect to efficacy. | ↑ | Consensus | Expert opinion |

| **Therapeutic combinations** | | Strength of consensus | Comments |
|---|---|---|---|
| Adalimumab | o | Consensus | No evidence available |
| Ciclosporin | ↓ | Strong consensus | Expert opinion: competition cytochrome P450 inactivation |
| Etanercept | ↑ | Consensus | Expert opinion: good safety profile assumed, possibly increased efficacy |
| Fumaric acid esters | o | Consensus | No evidence available |
| Infliximab | o | Consensus | No evidence available |
| Methotrexate | ↓ | Strong consensus | Expert opinion: increased risk of hepatotoxicity possible |
| Ustekinumab | o | Consensus | No evidence available |

Ciclosporin

| **Recommendation** | | Strength of consensus | Comment |
|---|---|---|---|
| If a short course for induction treatment is intended we recommend CSA. | ↑↑ | Strong consensus | Evidence and consensus based |
| For long-term treatment we suggest CSA only in selected patients. | ↑ | Strong consensus | Expert opinion |
| In case of continuous long-term treatment, we suggest CSA for a maximum of up to two years. | ↑ | Consensus | Expert opinion |
| In case a longer treatment is needed, we suggest the consultation with a nephrologist. | ↑ | Consensus | Expert opinion |
| Based on weighting of risk and benefit we suggest using CSA with a starting dose of 2.5 mg/kg bodyweight QD for up to four weeks, with a dosage increase up to 5 mg/kg bodyweight once daily thereafter. | ↑ | Weak con-sensus | Evidence and consensus based |

| Therapeutic combinations | | Strength of consensus | Comments |
|---|---|---|---|
| Acitretin | ↓ | Strong consensus | Expert opinion: competition cytochrome P450 inactivation |
| Adalimumab | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Etanercept | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Fumaric acid esters | o | Consensus | No evidence available |
| Infliximab | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Methotrexate | ↓ | Weak consensus | Expert opinion: increased risk of immunosuppression |
| Ustekinumab | ↓ | Consensus | Expert opinion: increased immunosuppression, anecdotal evidence of increased toxicity |

Fumarsäureester

| Recommendation | | Strength of consensus | Comment |
|---|---|---|---|
| We recommend fumaric acid esters for the induction treatment. | ↑↑ | Consensus | Evidence and consensus based |
| We recommend fumaric acid esters for the long-term treatment. | ↑↑ | Consensus | Expert opinion |
| We recommend fumaric acid esters with a slow increase dosing regimen. | ↑↑ | Consensus | Expert opinion |

| Therapeutic combinations | | Strength of consensus | Comments |
|---|---|---|---|
| Acitretin | o | Consensus | No evidence available |
| Adalimumab | o | Strong consensus | No evidence available |
| Ciclosporin | o | Consensus | No evidence available |
| Etanercept | o | Strong consensus | No evidence available |
| Infliximab | ↓ | Consensus | Expert opinion: increased risk |
| Methotrexate | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Ustekinumab | o | Consensus | No evidence available |

Methotrexat

| Recommendation | | Strength of consensus | Comment |
|---|---|---|---|
| We recommend MTX for the induction and long-term treatment. | ↑↑ | Strong consensus | Evidence and consensus based |
| Methotrexate can be given by oral or subcutaneous delivery. In general, a starting dose of 15 mg/week is used but individual dosages can range from 5 to 25 mg/week depending on individual factors. | Statement | Strong consensus | Expert opinion |

| Therapeutic combinations | | Strength of consensus | Comments |
|---|---|---|---|
| Acitretin | ↓ | Strong consensus | Expert opinion: increased risk of hepatotoxicity possible |
| Adalimumab | ↑ | consensus | Expert opinion: combination widely used in rheumatology; combination with low-dose MTX (e. g., 7.5 to 10 mg/week) is likely sufficient to reduce formation of anti-drug antibodies (ADA) and increase trough levels of adalimumab |
| Ciclosporin | ↓ | Weak consensus | Expert opinion: increased risk of immunosuppression |
| Etanercept | ↑ | consensus | Evidence (additional benefit of adding MTX to etanercept ocompared to etanercept monotherapy) and consensus based |
| Fumaric acid esters | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Infliximab | ↑ | Consensus | Expert opinion: combination widely used in rheumatology; combination with low-dose MTX (e. g., 7.5 to 10 mg/week) is likely sufficient to reduce formation of anti-drug antibodies (ADA) and increase trough levels of infliximab |
| Ustekinumab | o | Consensus | No evidence available |

Adalimumab

| Recommendation | | Strength of consensus | Comment |
|---|---|---|---|
| We recommend adalimumab as second line* medication for the induction and long-term treatment. | ↑↑ | Strong consensus | Evidence and consensus based |
| We recommend using adalimumab with an initial loading dose of 80 mg, week 1 40 mg followed by 40 mg every other week. | ↑ | Strong consensus | Expert opinion |

* if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated

| Therapeutic combinations | | Strength of consensus | Comments |
|---|---|---|---|
| Acitretin | o | Consensus | No evidence available |
| Ciclosporin | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Fumaric acid esters | o | Strong consensus | No evidence available |
| Methotrexate | ↑ | Consensus | Expert opinion: combination widely used in rheumatology; combination with low-dose MTX (e. g., 7.5 to 10 mg/week is likely sufficient to reduce formation of ADA and increase trough levels of adalimumab |
| Ustekinumab | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |

Etanercept

| Recommendation | | Strength of consensus | Comment |
|---|---|---|---|
| We recommend etanercept as second line* medication for the induction and long-term treatment. | ↑↑ | Strong consensus | Evidence and consensus based |
| In general, a starting dose of 50 mg once or twice weekly is used depending on individual factors. | Statement | Strong consensus | Expert opinion |
| For maintenance therapy 50 mg once weekly is a commonly used dose. | Statement | Strong consensus | Expert opinion |

* if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated.

| Therapeutic combinations | | Strength of consensus | Comments |
|---|---|---|---|
| Acitretin | ↑ | Consensus | Expert opinion: good safety profile assumed, possibly increased efficacy |
| Ciclosporin | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Fumaric acid esters | o | Strong consensus | No evidence available |
| Methotrexate | ↑ | Consensus | Evidence (additional benefit of adding MTX to etanercept compared to etanercept monotherapy) and consensus based |
| Ustekinumab | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |

Infliximab

| Recommendation | | Strength of consensus | Comment |
|---|---|---|---|
| We recommend infliximab as second line* medication for the induction and long-term treatment. | ↑↑ | Strong consensus | Evidence and consensus based |
| We recommend using infliximab 5 mg/kg bodyweight continuously every eight weeks during long-term treatment. | ↑↑ | Strong consensus | Evidence and consensus based |

* if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated.

| Therapeutic combinations | | Strength of consensus | Comments |
|---|---|---|---|
| Acitretin | o | Consensus | No evidence available |
| Ciclosporin | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Fumaric acid esters | ↓ | Strong consensus | Expert opinion: increased risk of immunosuppression, lymphocytopenia |
| Methotrexate | ↑ | Consensus | Expert opinion: combination widely used in rheumatology; combination with low-dose MTX (e. g., 7.5 to 10 mg/week is likely sufficient to reduce formation of ADA and increase trough levels of infliximab |
| Ustekinumab | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |

Ustekinumab

| Recommendation | | Strength of consensus | Comment |
|---|---|---|---|
| We recommend ustekinumab as second line* medication for the induction and long-term treatment. | ↑↑ | Strong consensus | Evidence and consensus based |
| We suggest using 45 mg for patients with a bodyweight of ≤ 100 kg and 90 mg ustekinumab for patients with a body weight of > 100 kg. | ↑ | Strong consensus | Evidence and consensus based |

* if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated (the label currently states: if PUVA or other systemic therapies including ciclosporin, methotrexate were inadequate in response or if they are contraindicated or not tolerated). No strong consensus on definition of 'second line' for usteki-numab was achieved, the definition passed with 'weak consensus' (55%).

| Therapeutic combinations | | Strength of consensus | Comments |
|---|---|---|---|
| Acitretin | o | Consensus | No evidence available |
| Adalimuab | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Ciclosporin | ↓ | Consensus | Expert opinion: increased immunosuppression, anecdotal evidence of increased toxicity |
| Etanercept | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Fumaric acid esters | o | Consensus | No evidence available |
| Infliximab | ↓ | Consensus | Expert opinion: increased risk of immunosuppression |
| Methotrexate | o | Consensus | No evidence available |

*Hiweis zur Leitlinie:*

- Keine gesonderten Empfehlungen für Kinder/Jugendliche

**NICE, 2012 [11].**
*National Institute for Health and Care Excellence (NICE)*
Psoriasis: assessment and management of psoriasis

**Leitlinienorganisation/Fragestellung**

This guideline aims to provide clear recommendations on the assessment and management of psoriasis for all people with psoriasis.

**Methodik**

Grundlage der Leitlinie:

NICE Guidelines Manual 2009 (Formulierung klinischer Fragestellungen und Endpunkte a priori, systematische Recherchen, Bewertung der Literatur anhand GRADE, Konsensusprozess ohne Beschreibung formaler Verfahren)

Recherche/Suchzeitraum:

- bis 8/03/2012, **Update 09/2017**

LoE

- nach GRADE

GoR

- sprachliche Formulierung

Sonstige methodische Hinweise

- The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.
- CoI declared
- nur wenige Empfehlungen speziell für moderate bis schwere Psoriasis formuliert

**Empfehlungen**

Topical therapy

- Offer people with psoriasis topical therapy as first-line treatment.
- Offer second- or third-line treatment options (phototherapy or systemic therapy) at the same time when topical therapy alone is unlikely to adequately control psoriasis, such as:
  - extensive disease (for example more than 10% of body surface area affected) or
  - at least 'moderate' on the static Physician's Global Assessment or
  - where topical therapy is ineffective, such as nail disease.

Phototherapy (broad- or narrow-band (UVB) light and PUVA)

- Offer narrowband ultraviolet B (UVB) phototherapy to people with plaque or guttate-pattern psoriasis that cannot be controlled with topical treatments alone. Treatment with narrowband UVB phototherapy can be given 3 or 2 times a week depending on patient preference. Tell people receiving narrowband UVB that a response may be achieved more quickly with treatment 3 times a week.
- Offer alternative second- or third-line treatment when:

  - narrowband UVB phototherapy results in an unsatisfactory response or is poorly tolerated or
  - there is a rapid relapse following completion of treatment (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months) or
  - accessing treatment is difficult for logistical reasons (for example, travel, distance, time off work or immobility) or
  - the person is at especially high risk of skin cancer.
- Consider psoralen (oral or topical) with local ultraviolet A (PUVA) irradiation to treat palmoplantar pustulosis.
- When considering PUVA for psoriasis (plaque type or localised palmoplantar pustulosis)
- discuss with the person:
  - other treatment options
  - that any exposure is associated with an increased risk of skin cancer (squamous cell carcinoma)
  - that subsequent use of ciclosporin may increase the risk of skin cancer, particularly if they have already received more than 150 PUVA treatments• that risk of skin cancer is related to the number of PUVA treatments.
- Do not routinely offer co-therapy with acitretin when administering PUVA.
- Consider topical adjunctive therapy in people receiving phototherapy with broadband or narrowband UVB who:
  - have plaques at sites that are resistant or show an inadequate response (for example, the lower leg) to phototherapy alone, or at difficult-to-treat or high-need, covered sites (for example, flexures and the scalp), and/or
  - do not wish to take systemic drugs or in whom systemic drugs are contraindicated.
- Do not routinely use phototherapy (narrowband UVB, broadband UVB or PUVA) as maintenance therapy.

<u>Systemic non-biological therapy</u>

- Offer systemic non-biological therapy to people with any type of psoriasis if:
  - it cannot be controlled with topical therapy and
  - it has a significant impact on physical, psychological or social wellbeing and
  - one or more of the following apply:

    psoriasis is extensive (for example, more than 10% of body surface area affected or a PASI score of more than 10) or

    psoriasis is localised and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites) or

    phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months).

[…]

**Choice of drugs**

- Offer methotrexate as the first choice of systemic agent for people with psoriasis who fulfil the criteria for systemic therapy except in the circumstances described in recommendations 1.5.2.4 and 1.5.2.12.
- In people with both active psoriatic arthritis and any type of psoriasis that fulfils the criteria for systemic therapy consider the choice of systemic agent in consultation with a rheumatologist.
- Offer ciclosporin as the first choice of systemic agent for people who fulfil the criteria for systemic therapy and who:
  - need rapid or short-term disease control (for example a psoriasis flare) or
  - have palmoplantar pustulosis or
  - are considering conception (both men and women) and systemic therapy cannot be avoided.
- Consider changing from methotrexate to ciclosporin (or vice-versa) when response to the first-choice systemic treatment is inadequate.
- Consider acitretin for adults, and in exceptional cases only for children and young people, in the following circumstances:
  - if methotrexate and ciclosporin are not appropriate or have failed or
  - for people with pustular forms of psoriasis.

Systemic biological therapy

[…]

**Adalimumab in adults**

The recommendations in this section are from Adalimumab for the treatment of adults with psoriasis (NICE technology appraisal guidance 146).

- Adalimumab is recommended as a treatment option for adults with plaque psoriasis for whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met.
  - The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10.
  - The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant of, or has a contraindication to, these treatments.
- Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either:
  - 75% reduction in the PASI score (PASI 75) from when treatment started or
  - 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment.

**Etanercept in adults**

The recommendations in this section are from Etanercept and efalizumab for the treatment of adults with psoriasis (NICE technology appraisal guidance 103).

- Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met.
  - The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10.
  - The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant to, or has a contraindication to, these treatments.
- Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either:
  - a 75% reduction in the PASI score from when treatment started (PASI 75) or
  - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started.

**Infliximab in adults**

The recommendations in this section are from Infliximab for the treatment of adults with psoriasis (NICE technology appraisal guidance 134).

- Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met.
  - The disease is very severe as defined by a total PASI of 20 or more and a DLQI of more than 18.
  - The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA, or the person is intolerant to or has a contraindication to these treatments.
- Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either:
  - a 75% reduction in the PASI score from when treatment started (PASI 75) or
  - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started.

**Ixekizumab in adults**

The recommendations in this section are from Infliximab for the treatment of adults with psoriasis (NICE technology appraisal guidance 442).

- Ixekizumab is recommended as an option for treating plaque psoriasis in adults, only if:
  - the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
  - the disease has not responded to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them, and
  - the company provides the drug with the discount agreed in the patient access scheme.
- Stop ixekizumab treatment at 12 weeks if the psoriasis has not responded adequately. An adequate response is defined as:

  - a 75% reduction in the PASI score (PASI 75) from when treatment started or
  - a 50% reduction in the PASI score (PASI 50) and a 5 point reduction in DLQI from when treatment started.
- When using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate.
- When using the DLQI, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate.
- These recommendations are not intended to affect treatment with ixekizumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

**Secukinumab in adults**

The recommendations in this section are from Infliximab for the treatment of adults with psoriasis (NICE technology appraisal guidance 350).

- Secukinumab is recommended, within its marketing authorisation, as an option for treating adults with plaque psoriasis only when:
  - the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
  - the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them
  - the company provides secukinumab with the discount agreed in the patient access scheme.
- Secukinumab treatment should be stopped in people whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these people. An adequate response is defined as either:
  - a 75% reduction in the PASI score from when treatment started (PASI 75) or
  - a 50% reduction in the PASI score (PASI 50) and a 5 point reduction in DLQI from when treatment started.
- People whose treatment with secukinumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
- When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate.

**Ustekinumab in adults**

The recommendations in this section are from Ustekinumab for the treatment of adults with moderate to severe psoriasis (NICE technology appraisal guidance 180).

- Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met.

  - The disease is severe, as defined by a total PASI score of 10 or more and a DLQI score of more than 10.
  - The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA, or the person is intolerant of or has a contraindication to these treatments.
  - The manufacturer provides the 90 mg dose (two 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial.
- Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either:
  - a 75% reduction in the PASI score (PASI 75) from when treatment started or
  - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI score from when treatment started.

Changing to an alternative biological drug

- Consider changing to an alternative biological drug in adults if:
  - the psoriasis does not respond adequately to a first biological drug as defined in NICE technology appraisals for etanercept, ixekizumab and secukinumab, and 16 weeks for adalimumab and ustekinumab; primary failure) or
  - the psoriasis initially responds adequately but subsequently loses this response, (secondary failure) or
  - the first biological drug cannot be tolerated or becomes contraindicated.
- For adults in whom there is an inadequate response to a second biological drug, seek supra-specialist advice from a clinician with expertise in biological therapy.

**Psoriasis in children and young people**

- Psoriasis in childhood is less common than adults. It tends to present in later childhood with a median age of onset between 7 and 10 years and an estimated UK prevalence of 0.71%. Since one third of adult patients with psoriasis present before 20 years of age they are an important group to consider in the overall disease management20. A positive family history of psoriasis is associated with a reduced age of onset of the disease. Paediatric practice tends to mirror that in adults, and in this guideline, recommendations relate to everyone with psoriasis irrespective of age, unless otherwise stated. The term ‘children’ refers to those up to 12 years, who become ‘young people’ thereafter, before merging with the adult population by 18 years of age. Within the recommendation, the term ‘people’ is used to encompass all ages. Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with psoriasis. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.
- Points of particular relevance to the paediatric population include the following:

- Plaque type psoriasis is also the most common form in the paediatric population. Other forms are guttate psoriasis with relapses following infections[326] and in very young children, less than two years of age, napkin psoriasis. This typically affects the inguinal folds and then spreads to involve the trunk and limbs[62].
- As with any condition occurring in children and young people, psoriasis may impact on the person's psychological and emotional development and educational needs. During adolescence, the impact of psoriasis can be especially challenging when issues around body image and appearance are particularly salient. All these aspects need to be considered in context of the individual, family and carers, and appropriate support provided. There is a lack of data on interventions in children and young people with psoriasis. The GDG agreed to base treatment recommendations on RCTs with extrapolation to children if no separate paediatric evidence was found. Any exceptions to this principle are noted in the LETR tables of the relevant review questions. Note that only two studies[62,295] that specifically addressed psoriasis in children were identified and included in the guideline.
- Psoriasis in children and young people is currently managed as part of the general paediatric dermatology case mix by consultant dermatologists who also care for children. There are no specialised paediatric psoriasis clinics although combined paediatric dermatology and rheumatology clinics are in existence in some centres to manage psoriasis and psoriatic arthritis in children. Due to the drug licensing restrictions, children with relatively mild disease are often referred to secondary care for treatment.
- Most topical agents have licensing restrictions from specific ages and systemic therapies are currently not licensed for the treatment of psoriasis in children of less than 16 years of age apart from Etanercept (the only biological therapy currently licensed for children of less than 16 years of age). Ultimately the prescriber must take responsibility for using drugs outside of their licensed indications but it is important to involve the parents and, if possible the child, in a discussion about risks and potential benefits, especially when considering interventions such as PUVA and systemic drugs. In all discussions with patients about their treatment the clinician should establish that the patient has the capacity[2] to make a fully informed decision about their care, and the ability to understand the potential benefits (and risks) of treatment.
- In the case of children, clinicians would normally involve those with parental responsibility in the clinical decision-making process. Clinicians should also consider the maturity and competence of the child to understand and make decisions about their own care. Children can consent to treatment when they are able to understand the risks and benefits but they cannot legally refuse treatment against their parents' wishes until they are 16 years old. It is important to consider the young person's cognitive developmental stage when discussing the disease and treatment options. Using appropriate terminology will help children and young people participate actively in decision-making.
- As children mature into young people and adults they should be encouraged to take more responsibility for managing their condition. Arrangements for transition to adult care (e.g. joint clinics with adult and paediatric dermatology teams) should be an integral part of the service. The relevant principles are considered in a Department of Health publication[75].
- When managing psoriasis in children and young people, treatment choice should be carefully considered to avoid or minimise long-term sequelae. This aspect is especially pertinent in relation to phototherapy.

Hinweis: The GDG agreed that in most situations it would be reasonable to extrapolate data from adult populations to children when there was no or little data. Therefore, the GDG agreed to base treatment recommendations on RCTs with extrapolation to children if no separate paediatric evidence was found. Any exceptions to this principle will be noted in the LETR tables

of the relevant review questions. Note that only two studies that specifically addressed psoriasis in children were identified and included in the guideline.

(…) None of the interventions, with the exception of topical calcipotriol, potent steroids (for those over 1 year of age) and acitretin, are licensed for use in psoriasis in children and there is little or no evidence in children.

(…) 38. Do not use very potent corticosteroids in children and young people.

(…) 70. Do not use PUVA when other appropriate treatments are available in:

- people with a personal history of skin cancer or
- people who have already received 150 PUVA treatments or
- children.

(…) 86. Consider acitretin for adults, and in exceptional cases only for children and young people, in the following circumstances:

- if methotrexate and ciclosporin are not appropriate or have failed or
- for people with pustular forms of psoriasis.

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**Fortina AB et al., 2017 [6].**

Treatment of severe psoriasis in children: recommendations of an Italian expert group.

**Leitlinienorganisation/Fragestellung**

Recommendations for the systemic treatment of severe pediatric psoriasis.

**Methodik**

Grundlage der Leitlinie

- Based on evidence obtained from a systematic review of the literature and the consensus opinion of expert dermatologists and pediatricians.
- For each systemic treatment, the grade of recommendation (A, B, C) based on the treatment's approval by the European Medicines Agency for childhood psoriasis and the experts' opinions is discussed (siehe unten)

Recherche/Suchzeitraum:

- literature search, encompassing studies published between January 2005 and January 2016, was conducted in Medline, EMBASE, and the Cochrane Library

LoE/GoR

- Levels of evidence and grades of recommendations (A–D) (Table 2) were determined according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence

| | |
|---|---|
| 1a | Systematic review of RCTs |
| 1b | Individual RCT |
| 2a | Systematic review of cohort studies |
| 2b | Individual cohort study (including low-quality RCT) |
| 3a | Systematic review of case-control studies |
| 3b | Individual case-control study |
| 4 | Case series |
| 5 | Case reports, expert opinion |

Adapted from the "Oxford Centre for Evidence-Based Medicine Levels of Evidence" version May 2001

*RCT* randomized controlled trial

| | |
|---|---|
| A | Studies with consistent LoE 1a and/or 1b |
| B | Studies with consistent LoE 2a, 2b, 3a, or 3b or extrapolations from studies with LoE 1a or 1b |
| C | Studies with LoE 4 or extrapolations from studies with LoE 2a, 2b, 3a, or 3b |
| D | Studies with LoE 5 or troublingly inconsistent or inconclusive studies of any level |

**Empfehlungen**

Phototherapy and systemic therapies: Grade C. (…) conclude that NB-UVB should not be suggested for toddlers and infants. Clinical experiences in children aged < 8 years are lacking. It should be considered for the treatment of children taking into account the patient's ability to collaborate and it should be used carefully, especially in patients with fair skin.

Retinoids: **Grade C.** Oral retinoids are not approved for the treatment of pediatric psoriasis. There are few studies on this issue and no conclusions can be drawn. Acitretin can be effective in pediatric patients with pustular psoriasis, taking into account the frequently reported side effects. Extreme caution is needed in women of child-bearing potential. Strict, appropriate monitoring for all possible side effects should be performed if treatment with oral retinoids is used.

Cyclosporine: **Grade C.** Cyclosporine A is not approved for pediatric psoriasis. It can be used in selected cases, preferably for a short period, with close monitoring for side effects.

Methotrexate: **Grade C/B.** Methotrexate is not approved for pediatric psoriasis. However, it can be used in all clinical forms and particularly in plaque psoriasis.

Etanercept: **Grade A.** Etanercept is approved by the EuropeanMedicines Agency for the treatment of children ≥ 6 years with severe, chronic plaque psoriasis after inadequate response to other systemic therapies or phototherapy. It is considered to be a second-line drug in severe plaque psoriasis in children, although no conventional first-line treatments are approved in the pediatric population.

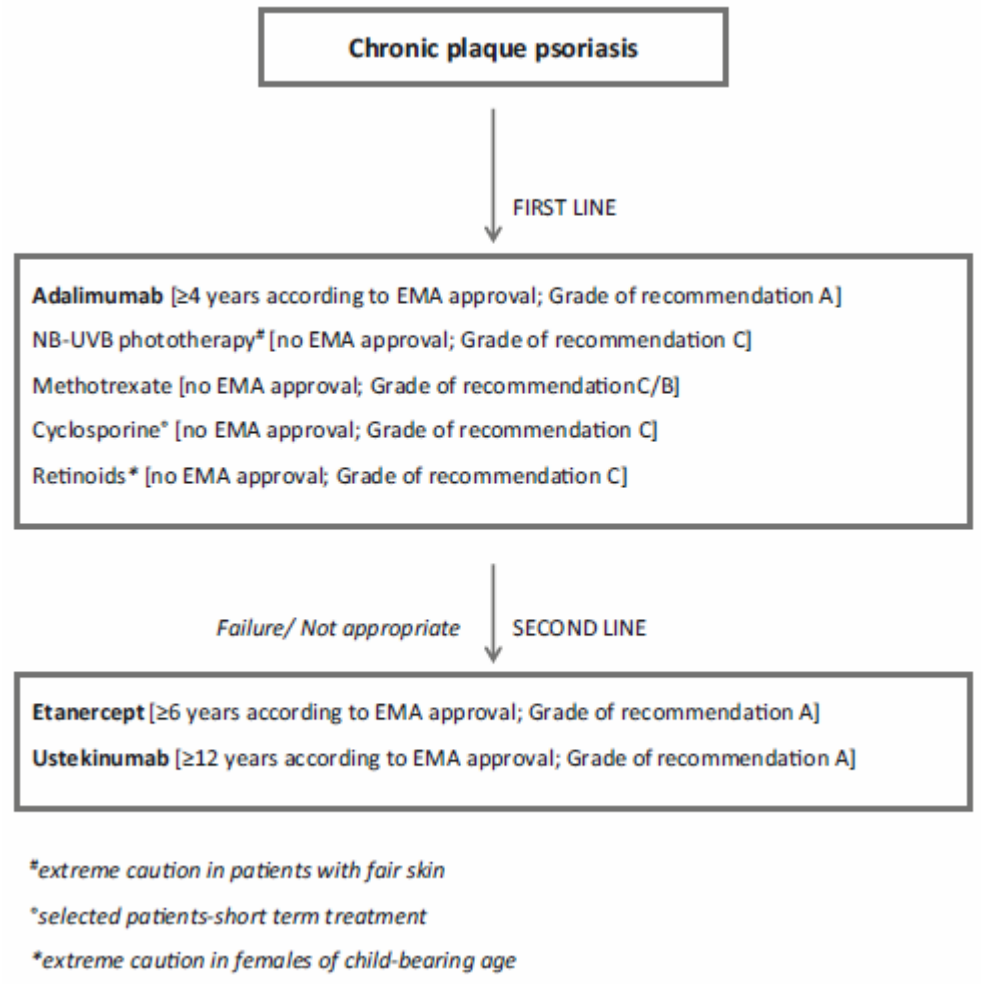
Adalimumab: **Grade A.** Adalimumab is approved by the European Medicines Agency as first-line treatment of severe chronic plaque psoriasis in children from 4 years of age and adolescents who are inappropriate candidates for topical therapy and phototherapy or have had an

inadequate response. It is considered a first-line treatment for severe plaque psoriasis in children.

Ustekinumab: **Grade A.** Ustekinumab has been approved by the European Medicines Agency for the treatment of children ≥ 12 years with severe, chronic plaque psoriasis after inadequate response to other systemic treatments or phototherapy. It is considered to be a second-line drug in severe plaque psoriasis in adolescents, although no conventional first-line treatments are approved for use in the pediatric population.

Infliximab: **Grade D.** Infliximab is not approved for the treatment of pediatric psoriasis. A solid conclusion regarding infliximab in the treatment of pediatric psoriasis could not be drawn.

**Algorithm for the systemic treatment and phototherapy of severe chronic plaque psoriasis in children according to the consensus of the expert group and EMA approval**



# 4 Detaillierte Darstellung der Recherchestrategie

### Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2018) am 20.12.2018

| # | Suchfrage |
|---|---|
| 1 | [mh Psoriasis] |
| 2 | psoriasis:ti,ab,kw |
| 3 | #1 or #2 |
| 4 | #3 with Cochrane Library publication date from Dec 2013 to Dec 2018 |

### Systematic Reviews in Medline (PubMed) am 20.12.2018

| # | Suchfrage |
|---|---|
| 1 | psoriasis[mh] |
| 2 | psoriasis[tiab] |
| 3 | (#1 OR #2) AND (((Meta-Analysis[ptyp] OR systematic review[pt] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab])))))) |
| 4 | ((#3) AND ("2013/12/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp])) |

**Leitlinien in Medline (PubMed) am 20.12.2018**

| # | Suchfrage |
|---|---|
| 1 | psoriasis [mh] |
| 2 | psoriasis[tiab] |
| 3 | (#1 OR #2) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])* |
| 4 | (((#3) AND ("2013/12/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp])) |

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# Anhang

**Tabelle 1:** EDF, 2015 [5]: Table 1: Strength of recommendations: wording, symbols and implications

| Strength | Wording | Symbols | Implications |
|---|---|---|---|
| Strong recommendation for the use of an intervention | "We recommend …" | ↑↑ | We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy. |
| Weak recommendation for the use of an intervention | "We suggest …" | ↑ | We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision making. Policy makers will have to involve many stakeholders and policy making requires substantial debate. |
| No recommendation with respect to an intervention | "We cannot make a recommendation with respect to …" | 0 | At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e. g., no evidence data available, conflicting outcomes, etc.) |
| Weak recommendation against the use of an interven- tion | "We suggest not (using) …" | ↓ | We believe that most informed people would make a choice against that intervention, but a substantial number would not. |
| Strong recommendation against the use of an interven- tion | "We recommend not (using) …" | ↓↓ | We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations. |