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GUIDELINES

Methods Report: European S3-Guidelines on the systemic treatment of psoriasis vulgaris – update 2015 – EDF in cooperation with EADV and IPC

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Abbreviations

AWMF: German Association of Scientific Medical Societies

CSA: Ciclosporine

COI: Conflicts of interest

dEBM: Division of Evidence Based Medicine

EADV: European Association for Dermatology and Venereology

EDF: European Dermatology Forum

IPC: International Psoriasis Council

MTX: Methotrexate

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1 Introduction

This document is the methods report to the 'Update of the evidence and consensus-based European S3-Guidelines of systemic treatment of psoriasis vulgaris'.

The first edition of these guidelines has been published in the Journal of the European Academy of Dermatology and Venereology.[1]

Please use the following reference when citing these guidelines: Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, Arenberger P, Bachelez H, Barker J, Dauden E, de Jong E, Feist E, Jacobs A, Jobling R, Kemeny L, Maccarone M, Mrowietz U, Papp KA, Paul C, Reich K, Rosumeck S, Talme T, Thio HB, van de Kerkhof P, Werner RN, Yawalkar N. European S3-Guidelines on the systemic treatment of psoriasis vulgaris - Update 2015 - Short version - EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol* 2015; **29**: 2277–2294.

The guidelines were developed taking into account the quality criteria for guidelines as suggested by the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument.[2] For the planning and elaboration of the underlying systematic literature review of interventions for psoriasis vulgaris, the methodology suggested by the Cochrane Handbook for Systematic Reviews of Interventions[3] and the GRADE working group[4] was adapted.

1.1 Remarks on the use of guidelines

These evidence- and consensus-based guidelines contain recommendations that were developed to assist clinicians in the care of patients in specific clinical conditions. The recommendations are based on the best available evidence and their development followed a pre-specified, standardized process. Nevertheless, guidelines do not replace the clinicians' knowledge and skills, since guidelines never encompass therapy specifications for all medical decision-making situations, deviation from the recommendations may be justified or inevitable in specific situations.

Safety aspects that were considered within these guidelines do not represent a comprehensive assessment of all available safety information for the included interventions. They are limited to those aspects chosen for evaluation and the information available in the included clinical trials. Readers must carefully check the information in these guidelines and determine whether the recommendations (e.g. regarding dose, dosing regimens,

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contraindications or drug interactions) are complete, correct, up-to-date and appropriate.

European guidelines are intended to be adapted to national or regional circumstances (regulatory approval and availability of treatments, health care provider and insurance systems). Thus, the national medical societies associated with the European Dermatology Forum (EDF) and the European Association for Dermatology and Venereology (EADV) will be responsible for the adoption and implementation of the guidelines on a national level.

1.2 Objectives of the guidelines

Aim was the update of the guidelines' version of 2009.[5] 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.

1.3 Target population

These guidelines are targeted at all health care professionals involved in the treatment of patients with psoriasis, primarily dermatologists and general practitioners (GP).

2 Methods

For the development of these evidence and consensus-based guidelines, the available evidence of the efficacy and safety of the systemic treatments for psoriasis was summarized. Based on the evidence, recommendations were formulated and consented by an expert panel in a structured consensus process.

2.1 Groups involved in the guidelines development

The Division of Evidence based Medicine (dEBM) from the Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Germany coordinated the guidelines development process including the organization of the guidelines process, development of methodology and the conduction of a systematic review of the literature on the systemic treatment of psoriasis vulgaris. Members of the dEBM participated in or moderated the consensus conference, but were not entitled to vote on recommendations.

Members of the expert group were dermatologists and a rheumatologist. They were officially nominated by the European Dermatology Forum (EDF), the European Association for Dermatology and Venereology (EADV) and the International Psoriasis Council (IPC). The expert group members were selected by virtue of their clinical experience and/or research expertise in the field of psoriasis vulgaris and their previous work on the first version of the European S3-Guidelines on the systemic treatment of psoriasis vulgaris in 2009.

An international patient organization to nominate representatives for patients affected by psoriasis vulgaris could not be identified, and thus patient participation was difficult to realize. Patient representatives from the UK and Italy each participated in the guidelines development process as a part of the expert group. These representatives had the same voting rights as the other members of the expert group and participated in the process of the internal review too. Furthermore one chapter, namely 'Severity assessment/Quality of life – Patients perspective' which is integrated in the main chapter 'introduction to psoriasis vulgaris' was written by the patient representatives. Patient reported outcomes such as DLQI scores were considered as a relevant outcome and studies reporting on these endpoints were included into the systematic literature review. Patients were invited to take part in the external review and to comment the drafted guidelines document.

A steering group of the guidelines project was composed by members of the expert group who have experiences in the field of guidelines development. The steering group was responsible for the selection of interventions, outcomes and relevant patient subgroups in the evidence assessment process.

A full list of the guidelines steering group and expert group members is supplied at the beginning of this document on page 2.

2.2 Funding of the guidelines and management of conflicts of interest

The guidelines project has kindly been supported by the EDF. The financial support did not influence the guidelines development. The expert group did not receive financial incentives or reimbursement for the participation in the guidelines development. Assessment and synthesis of the evidence were done independently from industrial interest. Key questions to be answered and outcomes were chosen in accordance to consensus of the members from the steering group. Recommendations on the systemic treatment of psoriasis vulgaris were exclusively based on the consensus of the members from the expert group in the consensus conference, according to the clinical expertise and evidence assessment.

A declaration of potential conflicts of interest (COI) adapted from the International Committee of Medical Journal Editors[6] was required for the participation in the guidelines development. At the beginning of the formalized consensus conference, each member was asked to update his or her declaration. COI were discussed. The expert group did not see any substantial conflicts of interest and there were no further comments or remarks. COI of each person involved in the guidelines development are presented in Appendix 4.1.

2.3 Summarizing the evidence of the systemic treatment

2.3.1 Selection of key questions to be answered The selection of key questions to be answered by guidelines is according to the previous version of the guidelines.[1,5] The following steps in the

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preparation of the systematic literature review were performed via electronic mail contacts and decided with the members of the expert group.

Selection of included interventions. The following treatment options were selected as relevant treatments for psoriasis vulgaris and included in the evaluation:

Monotherapies:

- Acitretin
- Ciclosporin (CSA)
- Fumaric acid ester
- Methotrexate (MTX)
- Adalimumab
- Etanercept
- Infliximab
- Ustekinumab

Although fumaric acid esters are licensed only in Germany, it is known that they are used in several other European countries as off-label medication (e.g. UK[7]) for psoriasis vulgaris and they are therefore included in the evidence-based assessment. The biological agent efalizumab[8] lost its marked authorization for psoriasis. Alefacept is licensed in Switzerland and the US only, but is currently not being distributed any more. Both medications were therefore excluded from the guidelines. Furthermore, the expert panel decided to exclude phototherapy due to the high number of studies for which the evidence work up was not feasible during this update (time and costs).

Following combination therapies were selected[1] :

- Included systemic therapy combined with another included systemic therapy
- Included systemic therapy + any topical treatment
- CSA + diet

Combinations of more than two treatment options were not considered. Studies on combination therapies were included if they compared the combination with the included systemic monotherapy to evaluate the benefit of the combination in comparison to the monotherapy.

The fact that certain treatments were not included does not necessarily imply that it may not be an appropriate treatment for psoriasis vulgaris.

Selection and rating of outcomes. The evaluation of the treatment options was based on efficacy, patient reported as well as safety outcomes. Beside these parameters, other outcomes were selected that seem to be of high importance to the patient.[9,10] According to the GRADE methodology, expert group members were asked to rate outcomes with respect to their relevance for clinical decisions concerning the choice of a treatment for psoriasis vulgaris on a scale from 1 to 9 with 1 representing irrelevant and 9 representing critical outcomes. Mean values of the ratings from the experts served to rank the importance of the selected outcomes when grading the available evidence. A mean score of 7–9 rated an outcome as critical for a decision, 4–6 rated an outcome as important but not critical for decision making, and a mean score of 1–3 indicated that the respective outcome was of limited importance.[11] Only critical and important outcomes were considered in the evidence assessment. Table 1 shows the selected outcomes and assigned rating of importance.

For reasons of feasibility and to ensure comparability, for the induction therapy the outcomes had to be reported at week 16 after the start of treatment or whatever was closest to that time point, however, not earlier than week 8.[12] For long-term therapy, the results had to be reported for week 24 or whatever was closest thereafter.

To be included into the systematic review, studies had to report at least one of the selected outcomes. Outcomes had to be reported as events per patients in case of dichotomous outcomes (the number of events and the number of patients at the time of assessment had to be reported) or as mean change in case of continuous outcomes (the mean and standard deviation had to be reported).

Table 1 Efficacy outcomes and assigned rating of importance

Outcome	Importance
Efficacy	
Induction therapy	
PASI 75 response	Critical
PASI 90 response	Important
Reduction in mean PASI/final PASI score	Important
Clearance (i.e. PGA 0, PASI 100, 'clear')	Important
PGA 0/1 (i.e. 'clear'/'almost clear')	Critical
Long-term therapy	
PASI 75 response	Critical
PASI 90 response	Critical
Reduction in mean PASI	Important
Clearance (i.e. PGA 0, PASI 100, 'clear')	Important
PGA 0/1 (i.e. 'clear/almost clear')	Critical
Safety	
Withdrawal due to adverse event	Critical
Number of patients with at least one adverse event	Important
Number of patients with at least one serious adverse events *(as listed in study)*	Critical
Patient reported	
Response in DLQI ≤ 5	Important
Reduction in mean DLQI	Important
Others	
Time till onset of action: time until 25% of patients achieve a PASI 75 response	Important
Time till onset of action: time until a 25% reduction in the mean baseline PASI is achieved	Important
Time to relapse (after discontinuation of treatment)	Important
Relapse rate at a given time point × in the publication	Important

[1]During consensus conference recommendations on combinations were given for the combinations of two included systemic treatments only.

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Eligibility criteria with respect to study type and population. Eligible studies for inclusion were initial RCTs (including placebo controlled or head-to-head trials) reporting on participants with a clinical diagnosis of psoriasis vulgaris independent of the publication type. A minimal number of 10 evaluated participants per study arm was required and a minimal treatment duration of 8 weeks. Publication language was not restricted.

Regarding the study population the following criteria were defined:

- Psoriasis vulgaris/plaque type psoriasis
- Adults (minimum of 18 years, or as defined in the study, e.g. 'adults')

At least 80% of the study participants need to fulfil the above mentioned population criteria.

2.3.2 Literature search: Search for guidelines and systematic reviews As these guidelines are an update of the previous version,[1,5] there was no systematic search for existing guidelines and systematic reviews on systemic treatments of psoriasis vulgaris.

2.3.3 Literature search: Update search for primary literature A systematic literature search was performed to update the previous guidelines using the databases Cochrane Library, Medline, Medline In-Process and Embase on September 12th 2013. Start date was the particular inception date of each database. Automatic e-mail alerts by all four databases with new hits for the entire search strategy were received monthly up to October 12th 2014. Detailed electronic search strategies for the different databases are presented in the Appendix (see chapter 4.2).

Titles and abstracts of the search were individually checked for eligibility by two independent assessors (AJ, SR). Full texts of potentially relevant studies were similarly checked for eligibility by two independent assessors (AJ, SR). In the case of disagreement during the screening of abstracts and full texts, a third assessor (AN) was involved and the conflict solved by discussion (Fig. 1).

2.3.4 Data extraction Data collection of the literature search results was done independently by two assessors (AJ, SR), using a standardized data extraction form (Microsoft® Excel worksheet, Table 2). All relevant outcome data were then transferred in a Review Manager file.[13]

2.3.5 Data analysis Risk ratios with 95% CI for dichotomous data and mean differences with 95% CI for continuous data were calculated for each study comparison.

In case of continuous data with missing standard derivation (SD), SD was calculated from standard error or confidence interval if available. No other SD imputation

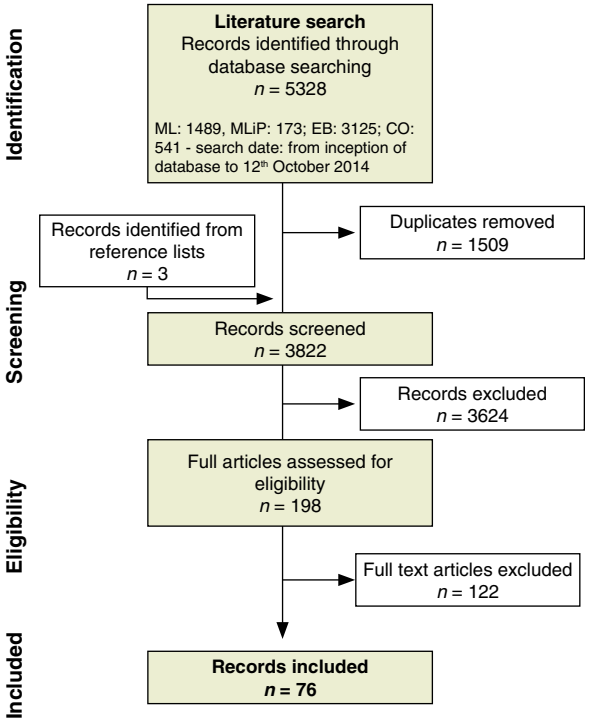

Figure 1 Flow of information through the different phases of the systematic literature search. ML, Medline, MLiP, Medline In-Process, EB, Embase, CO, Cochrane Library.

methods were performed and results from comparisons without any measure of variance were not considered for meta-analysis.

The effect estimates of the individual studies were pooled in meta-analysis using the random effects model (Review Manager 5.2). We included numerous multi-arm studies in our analyses. If multiple comparisons of one study were included into one meta-analysis, we split the shared group into two or three groups with smaller sample size to avoid double-counting of the participants that would create a unit-of-analysis error.

Studies with no events in both arms were excluded from the meta-analysis, because they do not provide any information of either the direction or magnitude of the relative treatment effect[3].

Limited placebo controlled data were available for long-term treatment. Most of the long-term studies 'loose' their placebo group after the induction period. Only three long-term studies were identified that provide placebo controlled data for week 24. To include long-term data from studies without a long-term placebo group, long-term placebo data from the three studies were pooled to calculate the 'placebo response'. Based on the original size of the 'lost' placebo arms, placebo values for long-time studies with lost placebo

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Table 2 Standardized data extraction form

General information	First author
	Year
	Intervention
	comparison
	Sponsorship
Study characteristic	Number (*n*) randomized per group
	Study duration [w]
	Concurrent treatment
	Washout phase
Inclusion criteria	Minimal PASI
	Age
	Previous treatment required?
Baseline characteristics	Age [mean/median (range/SD)]
	PASI [mean (SD/range)
	DLQI [mean (SD/range)]
	Female [%]
	Weight [kg (SD, range)]
Withdrawals	Number of withdrawals with >= 1 dose
	due to AE in induction therapy
	due to AE in long-term therapy
Cochrane risk of bias	Sequence generation
	Allocation concealment
	Comment: allocation concealment
	Comment: blinding of patients
	Blinding of personnel and outcome
	Incomplete outcome data
	Selective outcome reporting
	Other sources of bias
Results	
Induction: PASI response	Time of assessment [w]
	PASI 75
	PASI 90
Induction: mean PASI	Time of assessment [w]
	N
	mean PASI [±SD]
	mean PASI reduction from BL [± SD]
Induction: PGA	Time of assessment [w]
	Clear (PGA 0, PASI 100)
	Clear/almost clear (PGA 0/1)
Induction: DLQI	Time of assessment [w]
	N
	DLQI ≤ 5
	mean DLQI [± SD]
	mean reduction in DLQI [± SD]
Time until onset of action	TOA 25 PASI 75 [w]
	TOA 25% mean PASI [w]
Long-term: PASI response	Time of assessment [w]
	PASI 75
	PASI 90
	Time of assessment [w]
	PASI 75
	PASI 90
Long-term: mean PASI	Time of assessment [w]
	N
	mean PASI [±SD]
	mean PASI reduction from BL [± SD]
Long-term: PGA	Time of assessment [w]
	Clear (PGA 0, PASI 100)
	Clear/almost clear (PGA 0/1)
Long-term: DLQI	Time of assessment [w]
	N
	DLQI ≤ 5
	mean DLQI [± SD]
	mean reduction in DLQI [± SD]
Relapse	Median time to relapse (w)
	Relapse rate at time ×
AE induction	Time of assessment [w]
	Number of patients with at least 1 AE
AE long-term	Time of assessment [w]
	Number of patients with at least 1 AE
SAE induction	Time of assessment [w]
	Number of patients with at least 1 SAE
SAE long-term	Time of assessment [w]
	Number of patients with at least 1 SAE
Comments	

Table 3 Available placebo outcome data for week 24

Study	Comparator to placebo	Placebo response		
		PASI75	PASI90	PGA "clear/almost clear"
Gottlieb 2003	etanercept	3/55	0/55	not available
Reich 2005	infliximab	3/77	1/77	2/55
Asahina 2010	adalimumab	6/46	2/46	5/46
Total placebo response (absolute)		12/178	3/178	7/101
Total placebo response (%)		**6.7**	**1.7**	**6.9**

groups were imputed using the pooled placebo response. Placebo data were available for PASI75, PASI90 and PGA 'clear/almost clear'. Identified placebo data at week 24 are provided in Table 3.

The method used to calculate the mean time until onset of action (TOA 25 PASI 75 [w] and TOA 25% mean PASI [w]) is described elsewhere.[9] A drug was assessed to have a *slightly faster* onset of action than its comparator if the difference of time was > 0.5 weeks; a *faster* onset of action was described by a difference of > 1 week.

2.3.6 Quality assessment of the evidence The quality of the included studies was assessed by using the Cochrane Risk of bias tool.[3] The available evidence and its quality were summarized

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Table 4 Summary of the approach used to grade the quality of evidence for each outcome of interest and the quality levels of evidence as suggested by the GRADE working group[15]

Source of body of evidence and initial rating of quality of a body of evidence		Factors that may decrease the rating	Factors that may increase the rating	Final quality of the body of evidence for a certain recommendation and implications	
RCT	**High**	1. Limitations to study quality 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias	1. Large effect 2. Dose–response 3. All plausible confounding would have reduced the demonstrated effect	**High (++++)**	We are very confident that the true effect lies close to that of the estimate of effect.
				Moderate (+++)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Observational studies*	**Low**			**Low (++)**	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
				Very low (+)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*Observational studies were not included in the evidence-based assessment of these Guidelines (see chapter 2.3.1 paragraph 'Eligibility criteria with respect to study type and population').

according to the system recommended by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group[4] for each available outcome in each comparison.

Using the GRADE profiler,[14] GRADE evidence profiles were developed for each available treatment comparison, based on the rated outcomes (see chapters 2.3.1). The quality of the evidence for each key question was categorized into one of four categories, from 'very low' to 'high'.[15]

Table 4 summarizes the different quality levels of evidence and the approach used to grade the quality of evidence as suggested by the GRADE working group.[15]

The following criteria, as presented by the GRADE working group were applied to decrease or increase the quality ratings for each key question, intervention and outcome:

Limitations to the study quality. The Cochrane risk of bias tool[3] was used to assess limitations to the study quality on a study level. The following domains were assessed: random sequence generation, allocation concealment, incomplete outcome data, selective reporting, blinding of participants and personnel, blinding of outcome assessment and other sources of bias. Overall study quality depended on the limitations of the contributing studies. A downgrading of 1 ('serious limitations') or 2 points ('very serious limitations') was possible.[16] In addition to these criteria quality was downgraded by two points in case of imputed placebo group data.

Inconsistency. Overall quality of evidence was downgraded by 1 point ('important inconsistency'), when the study results were heterogeneous with respect to the direction or the size of the effect. The main criteria for downgrading were: widely varying point estimates across the studies, minimal or no overlap of the confidence intervals (CI), large I^2 (I^2 is a statistical test quantifying the variation in the point estimate between the studies).[17] Inconsistency could not be assessed in case of only one contributing study and no downgrading was performed.

Indirectness. When differences between the effect size in the populations recruited for the study participation and the patient subgroup to make a recommendation for were expected (due to significant and important differences in the studied populations to the target population), overall study quality was downgraded by 1 ('some') or 2 points ('major uncertainty about the directness').[18] Here, study quality was downgraded, when the study inclusion criteria or the patient characteristics at baseline did not match exclusively one of the predefined patient subgroups (e.g. study population consist of patients with mild psoriasis).

Imprecision. The main criterion for determining the precision of the pooled effect size is the width and position of the 95% confidence interval (CI)[19]: the overall study quality was downgraded for imprecision if the CI was very wide, crossed the threshold of minimal important difference (defined as the line of no effect $\pm$ 0.25) or if the CI crossed the line of no effect and the threshold of minimal important difference. For continuous outcomes such as the mean reduction in PASI, the minimal important difference was calculated as the line of no effect $\pm$ 0.5*SD of the control group.

For outcome data calculated in secondary analysis (i.e. TOA) the quality of evidence was downgraded twice, because no mea-

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sure of variance was available and the degree of imprecision therefore not estimable.

Publication bias. When publication bias was expected to influence the size or direction of the effect, study quality was downgraded by 1 point.[20] Due to the low number of contributing trials for each comparison, no formal testing (e.g. visual characterization of funnel plots) could be performed.

Large effect/evidence of dose–response gradient/confounders that would have decreased the effect. Rating up the quality of evidence due to the mentioned reasons is generally recommended only to be applied to results from observational studies or non-randomized trials.[21] As the systematic literature search was restricted to randomized controlled trials, no upgrading of the overall study quality was performed.

The quality of the evidence was evaluated by two assessors (AJ, SR) after discussion of each aspect. Comments to justify the ratings are supplied in case of downgrading.

2.3.7 Presentation of the results For each comparison of interventions, a short text summarizing the available evidence and a GRADE summary of findings table is presented in the guidelines. Data are presented as risk ratios (dichotomous outcomes)[22] or mean differences (continuous outcomes).[23]

The summary of finding tables served as the basis for developing the treatment recommendations.

2.4 Special considerations and special patient populations

In addition to the recommendation for the general psoriasis patient population, the guideline provides recommendations for special considerations and special patients:

- Tuberculosis screening before and during biological treatment
- Hepatitis/other hepatological dysfunctions
- HIV
- Malignancies including lymphoma and skin cancer
- Neurological disease
- Ischaemic heart disease and congestive heart failure
- Diabetes mellitus
- Kidney failure/Renal impairment
- Wish for pregnancy in near future
- Psoriasis arthritis
- Vaccination

The recommendations for subchapters are not based on systematically assessed literature and represent expert opinions. Although topicals and UV are not the focus of the guideline, the group decided on mentioning them for these subpopulation, where they are highly relevant as first line treatments.

2.5 Development of recommendations/consensus process

Prior the consensus conference, the draft of the guideline including the results of the systematic literature review was circulated in the expert group. Using the Delphi technique a first voting on the drafts of recommendations on drugs and on therapies in special patient populations was performed and alternative suggestions were collected where required.

During the consensus conference performed on October 9th and 10th in Amsterdam, The Netherlands, the formal consensus methodology of the nominal group technique was used to agree upon the recommendations.[24] All expert group members were entitled to vote on the recommendations. The nominal group technique was moderated by Alexander Nast, MD, certified moderator for the German Association of Scientific Medical Societies (AWMF).

To simplify the identification of consented recommendations, all consented recommendations are highlighted throughout the guidelines document (grey boxes). To avoid ambiguity, a standardized language was used to classify the direction and strength of each recommendation.

Based on the GRADE approach, five strengths of recommendations were differentiated: strong recommendations for or against the use of an intervention, weak recommendations for or against the use of an intervention, and no recommendation.[25] The strength of a recommendation based on the quality of the evidence (high/moderate/low/very low), the balance of expected undesirable and desirable outcomes and consideration of costs as well as of values and preferences.[25,26] The strength of recommendation was expressed by the wording and symbols (Table 5).

For each recommendation, the strength of consensus in terms of percentage of agreement was measured and documented. Three levels of consensus were defined and distinguished. A 'strong consensus' defined as an agreement of at least 95% of the members of the expert group was generally aimed at. In cases where only lower values of agreement were achieved, these were defined as 'consensus' (75–94% agreement) or 'weak consensus' (50–74% agreement).

The sections 'Instructions for use' and 'Lab control' of each medication were discussed and consented as a whole within the expert group, at which no strength of recommendation was provided in the guidelines text.

2.6 Peer review and piloting

Before publication, the guidelines draft underwent an extensive internal and external review.

Internal review was accomplished at the beginning of the guidelines development to confirm the selection of key questions (kick-off conference), prior to the consensus conference for a preliminary review of the results from the systematic literature review, after the consensus conference to confirm the completed

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Table 5 Strength of recommendations: wording, symbols and implications[25,26]

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 . . .'	o	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 intervention	'We suggest not . . .'	↓	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 intervention	'We recommend not . . .'	↓↓	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

recommendations, and after the external review to confirm changes before publication.

The EDF disseminated the draft to its members for external review. The external review was performed in cooperation with the EADV, UEMS and IPC. In addition, any other interested individual was free to participate in the external review, as the guidelines draft was accessible online for open comments from 27th January 2015 through 23rd February 2015 (using the platform www.crocodoc.com). Each comment was categorized as 'editorial change', 'forwarded to authors for consideration' or 'rejected (including reasoning)'. This document with all responses is available at the dEBM.

As a result of the comments and suggestions of the external review the expert group re-voted on three issues using a modified Delphi technique. These were namely (i) blood count monitoring in therapy with fumaric acid esters, (ii) instruction for use for woman of childbearing age after etanercept therapy and (iii) the definition of 'second line' in the footnote of the treatment recommendation of ustekinumab. For the results of re-voting, see final version of guidelines text.

During the phase of external review, the members of the expert panel piloted the drafted guidelines within their own practices and were encouraged to comment on the practicability and results during the second internal review.

European guidelines are intended to be adapted to the national circumstances of each health system.

2.7 Implementation, evaluation, updating

European guidelines are intended to be adapted to national or regional circumstances (regulatory approval and availability of treatments, health care provider and insurance systems). Thus, the national medical societies associated to the EDF will be responsible for the adaption and implementation of the guidelines on a national level. The guidelines publication and this methods report will be published online (http://www.euroderm.org/index.php/edf-guidelines). Evaluation strategies with respect to the awareness of the treatment necessity among patients and physicians, the treatment adhesion and treatment success should be pursued at a national level.

Due to the increasing amount of publications, guidelines need to be continually updated to reflect the recent state of evidence. After December 31st, 2019, these guidelines will expire. Should important changes occur in the meantime (such as new available interventions, new important evidence or withdrawal of drug licensing) the information may expire earlier. In these cases, an update issue of the guidelines is needed earlier. The EDF will be responsible to initiate an update.

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4 Appendices

4.1 Declarations of conflicts of interest

		Arenberger, Petr	Bachelez, Hervé	Barker, Jonathan	Dauden, Esteban	de Jong, Elke
1	**Work under consideration for these Guidelines**					
1.1	Grant	No	No	No	No	No
1.2	Consulting fee or honorarium	No	No	No	No	No
1.3	Support for travel to meetings for the study or other purposes	No	No	No	No	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees and the like	No	No	No	No	No
1.5	Payment for writing or reviewing the manuscript	No	No	No	No	No
1.6	Provision of writing assistance, medicines, equipment or administrative support	No	No	No	No	No
1.7	Other	No	No	No	No	No
2	**Relevant financial activities outside submitted work**					
2.1	Board membership	No	No	Personally: Amgen, Lilly, Novartis, Pfizer, Abbvie, Janssen, Creabilis	Personally: Abott/Abbvie, Janssen-Cilag, LEO Pharma, Novartis, Pfizer	No
2.2	Consultancy	No	Personally: Abbvie, Amgen, Boehringer, Celgene, Eli Lilly, Janssen, Leo Pharma, MSD, Novartis, Pfizer, Takeda	Personally: Amgen, Lilly, Novartis, Pfizer, Abbvie, Janssen, Creabilis	No	Institution: (inter) national consultancies for companies manufacturing treatments for prosiasis: Pfizer, AbbVie, Janssen
2.3	Employment	No	No	No	No	No
2.4	Expert testimony	No	No	No	No	No
2.5	Grants/grants pending	Personally/institution: Ministry of Health Czech Republic	Institution: Pfizer	Institution: Pfizer	Institution: Abbott/Abbvie, Janssen-Cilag, Pfizer, MSD	Institution: companies manufacturing treatments for prosiasis for investigator initiated research: Pfizer, AbbVie, Janssen
2.6	Payment for lectures including service on speakers bureaus	Personally: AbbVie, BMS, Novartis, Pfizer, Leo, GSK, Sandoz	Personally: Abbvie, Amgen, Boehringer, Celgene, Eli Lilly, Janssen, Leo Pharma, MSD, Novartis, Pfizer, Takeda	Personally: Amgen, Lilly, Novartis, Pfizer, Abbvie, Janssen, Creabilis	Personally: Abbott/Abbvie, Janssen-Cilag, Pfizer, MSD, LEO Pharma, Celgene	Institution: companies manufacturing treatments for prosiasis: Pfizer, AbbVie, Janssen, MSD

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Appendix 4.1 *(Continued)*

		Arenberger, Petr	Bachelez, Hervé	Barker, Jonathan	Dauden, Esteban	de Jong, Elke
2.7	Payment for manuscript preparation	No	No	No	No	No
2.8	Patents (planned, pending or issued)	No	No	No	No	No
2.9	Royalties	No	No	No	No	No
2.10	Payment for development of educational presentations	No	No	Personally: Janssen	No	Institution: AbbVie
2.11	Stock/stock options	No	No	No	No	No
2.12	Travel, accommodations and meeting expenses unrelated to activities listed	No	Personally: Janssen, Pfizer	No	No	No
2.13	Other (err on the side of full disclosure)	No	No	No	No	No
3	**Other relationships**	**No**	**No**	**No**	**No**	**No**
		Feist, Eugen	**Gisondi, Paolo**	**Jacobs, Anja**	**Jobling, Raymond**	**Kemeny, Lajos**
1	**Work under consideration for these guidelines**					
1.1	Grant	No	No	Institution: European Dermatology Forum	No	No
1.2	Consulting fee or honorarium	No	No	No	No	No
1.3	Support for travel to meetings for the study or other purposes	No	No	No	No	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees and the like	No	No	Institution: European Dermatology Forum	No	No
1.5	Payment for writing or reviewing the manuscript	No	No	Institution: European Dermatology Forum	No	No
1.6	Provision of writing assistance, medicines, equipment or administrative support	No	No	No	No	No
1.7	Other	No	No	No	No	No
2	**Relevant Financial Activities Outside Submitted Work**					
2.1	Board membership	Personally: Novartis, Pfizer, BMS	No	No	No	Personally: Janssen, Abbvie, MSD, Novartis
2.2	Consultancy	No	No	No	No	No
2.3	Employment	No	No	No	No	No
2.4	Expert testimony	No	No	No	No	No

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Appendix 4.1 *(Continued)*

		Feist, Eugen	Gisondi, Paolo	Jacobs, Anja	Jobling, Raymond	Kemeny, Lajos
2.5	Grants/grants pending	No	No	Institution: Stiefel	No	No
2.6	Payment for lectures including service on speakers bureaus	Personally: Novartis, Pfizer, Abbvie, MSD	Personally: Pfizer, Janssen, Abbvie, Merck Sharp, Dome	No	Institution (The Psoriasis Association): LEO Pharma & Janssen (Jan and Nov 2010)	Personally: Janssen, Abbvie, Pfizer, MSD, Galderma, Novartis
2.7	Payment for manuscript preparation	No	No	No	No	No
2.8	Patents (planned, pending or issued)	No	No	No	No	No
2.9	Royalties	No	No	No	No	No
2.10	Payment for development of educational presentations	No	No	No	No	No
2.11	Stock/stock options	No	No	No	No	No
2.12	Travel, accommodations and meeting expenses unrelated to activities listed	No	No	No	No	No
2.13	Other (err on the side of full disclosure)	No	No	No	Institution (The Psoriasis Association): Pharma companies (Abbvie, Dermal Laboratories Ltd, Forest Laboratories Ltd, Galderma [Uk] Ltd, Janssen, Leo Pharma, Novartis, T and R Derma) paid a fee for corporate memberships and non-recurrent grants for educational purposes	No
3	**Other relationships**	**No**	**No**	**No**	**No**	**No**

		Maccarone, Mara	Mrowietz, Ulrich	Nast, Alexander	Ormerod, Anthony	Papp, Kim	Paul, Carle
1	**Work Under Consideration for these Guidelines**						
1.1	Grant	No	No	Institution: European Dermatology Forum	No	No	No
1.2	Consulting fee or honorarium	No	No	No	No	No	No
1.3	Support for travel to meetings for the study or other purposes	No	No	No	No	No	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees, and the like	No	No	Institution: European Dermatology Forum	No	No	No

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Appendix 4.1 *(Continued)*

		Maccarone, Mara	Mrowietz, Ulrich	Nast, Alexander	Ormerod, Anthony	Papp, Kim	Paul, Carle
1.5	Payment for writing or reviewing the manuscript	No	No	Institution: European Dermatology Forum	No	No	No
1.6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No	No	No
1.7	Other	No	No	No	No	No	No
2	**Relevant Financial Activities Outside Submitted Work**						
2.1	Board membership	No	Personally: Abbott/ AbbVie, Biogen Idec, Centocor, Eli Lilly, Forward Pharma, MSD, Miltenyi Biotech, Novartis, Pfizer	Personally: Pfizer Pharma	No	No	No: EADV (Secretary general)
2.2	Consultancy	No	Personally: Abbott/ AbbVie, Almirall-Hermal, Amgen, BASF, Biogen Idec, Celgene, Centocor, Eli Lilly, Forward Pharma, Galderma, Janssen, Leo Pharma, Medac, MSD, Miltenyi Biotech, Novartis, Pfizer, Teva, VBL, Xenoport	No	Personally: Amgen	Personally/Institution: 3M, Abbott, Alza, Amgen, Astellas, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Janssen, Janssen Biotech(Centocor), J&J, Kirin, Merck, Novartis, Pfizer, UCB,	Personally: Astellas, Pierre Fabre, Sanofi, Abbvie, Amgen, Celgene, Janssen, Leo, Lilly, Novartis, Pfizer (Consultancy in the field of clinical research and data review)
2.3	Employment	No	No	No	No	No	No
2.4	Expert testimony	No	No	Personally: Sanofi Germany	No	No	No
2.5	Grants/grants pending	No	Institution: Abbvie, Novartis, Leo-Pharma	Institution: Stiefel (GlaxoSmithKline group), Biogen Idec, Intendis GmbH	Institution: Novartis, Pfizer, Merk, Abbvie	No	Institution: GSK, Pfizer, Pierre Fabre (Grant for clinical research work)
2.6	Payment for lectures including service on speakers bureaus	No	Personally: Abbott/ AbbVie, Almirall-Hermal, Biogen Idec, Janssen, Leo Pharma, Medac, MSD, Novartis, Pfizer	Personally: Biogen Idec, AbbVie Germany, Pfizer Pharma, Abbott Laboratories, Leo Pharma, Synergy, Sinclair Pharma, Universitätsklinikum Schleswig-Holstein, Klinik für Dermatologie	No	Personally/Institution: 3M, Abbott, Amgen, Astellas, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Galdema, Janssen, Merck, Novartis, Pfizer	Personally: Abbvie, Celgene, Pfizer (Lectures at scientific symposia)
2.7	Payment for manuscript preparation	No	No	Personally: Intendis GmbH	No	No	No

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Appendix 4.1 *(Continued)*

		Maccarone, Mara	Mrowietz, Ulrich	Nast, Alexander	Ormerod, Anthony	Papp, Kim	Paul, Carle
2.8	Patents (planned, pending, or issued)	No	No	No	No	No	No
2.9	Royalties	No	No	No	No	No	No
2.10	Payment for development of educational presentations	No	No	Personally: Biogen Idec, AbbVie Germany, Intendis GmbH, Pfizer Pharma, Abbott Laboratories, Leo Pharma, Synclair Pharma, Universitätsklinikum Schleswig-Holstein, Klinik für Dermatologie	No	No	Personally: Abbvie (Psoriasis educational slides)
2.11	Stock/stock options	No	Personally: Forward Pharma	No	No	No	No
2.12	Travel, accommodations, and meeting expenses unrelated to activities listed	No	No	Personally: Universitätsklinikum Carl Gustav Carus (Dresden), Psoriasis International Network, Deutsche Dermatologie Gesellschaft, Universitätsklinikum Erlangen, European Dermatology Forum, Universitätsklinikum Schleswig-Holstein, Universitätsklinikum München, International Psoriasis Council	Personally: Novartis	No	Personally: Janssen (Support for attending AAD 2012)

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Appendix 4.1 *(Continued)*

		Maccarone, Mara	Mrowietz, Ulrich	Nast, Alexander	Ormerod, Anthony	Papp, Kim	Paul, Carle
2.13	Other (err on the side of full disclosure)	No	No	Institution: Galderma Laboratorium GmbH, Ipsen Pharma GmbH, Allergan, Kythera Biopharmaceuticals, Deutsche Dermatologische Gesellschaft, Deutsche Gesellschaft für Dermatochirurgie, Paul-Ehrlich-Gesellschaft für Chemotherapie e.V., Deutsche Gesellschaft für Radioonkologie e.V., Deutsche Forschungsgemeinschaft	No	No	No
3	**Other relationships**	**No**	**No**	**No**	**No**	**No**	**No**

		Reich, Kristian	Rosumeck, Stefanie	Saiag, Philippe	Smith, Catherine	Spuls, Phyllis
1	**Work under consideration for these guidelines**					
1.1	Grant	No	Institution: European Dermatology Forum	No	No	No
1.2	Consulting fee or honorarium	No	No	No	No	No
1.3	Support for travel to meetings for the study or other purposes	No	No	No	No	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees and the like	No	Institution: European Dermatology Forum	No	No	No
1.5	Payment for writing or reviewing the manuscript	No	Institution: European Dermatology Forum	No	No	No
1.6	Provision of writing assistance, medicines, equipment or administrative support	No	No	No	No	No
1.7	Other	No	No	No	No	No
2	**Relevant financial activities outside submitted work**					

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Appendix 4.1 *(Continued)*

		Reich, Kristian	Rosumeck, Stefanie	Saiag, Philippe	Smith, Catherine	Spuls, Phyllis
2.1	Board membership	Personally: AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, MSD, Novartis, Ocean Pharma, Pfizer, Takeda, Vertex	No	Personally/institution: Roche, GSK, BMS, MSD	No	Institution: Leopharma (Dovobet), Novartis (Omalizuma), Anacor
2.2	Consultancy	Personally: AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, MSD, Novartis, Ocean Pharma, Pfizer, Takeda, Vertex	No	Personally: Roche, GSK, BMS	No	Institution: AbbVie (biosimilars)
2.3	Employment	No	No	No	No	No
2.4	Expert testimony	Personally: AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, MSD, Novartis, Ocean Pharma, Pfizer, Takeda, Vertex	No	No	No	No
2.5	Grants/grants pending	Institution: Novartis, MEDA, Takeda	Institution: Stiefel, Intendis	Institution: Roche	No	Institution: Leopharma
2.6	Payment for lectures including service on speakers bureaus	Personally: AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, MSD, Novartis, Ocean Pharma, Pfizer, Takeda, Vertex	No	Personally: Roche, GSK, BMS	No	No
2.7	Payment for manuscript preparation	No	No	No	No	No
2.8	Patents (planned, pending, or issued)	No	No	No	No	No
2.9	Royalties	No	No	No	No	No

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Appendix 4.1 *(Continued)*

		Reich, Kristian	Rosumeck, Stefanie	Saiag, Philippe	Smith, Catherine	Spuls, Phyllis
2.10	Payment for development of educational presentations	Personally: AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, MSD, Novartis, Ocean Pharma, Pfizer, Takeda, Vertex	No	Personally: Roche, GSK, BMS	No	No
2.11	Stock/stock options	No	No	No	No	No
2.12	Travel, accommodations and meeting expenses unrelated to activities listed	Personally: AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, MSD, Novartis, Ocean Pharma, Pfizer, Takeda, Vertex	No	Personally: Roche, GSK, BMS	No	No
2.13	Other (err on the side of full disclosure)	No	Institution: Galderma Laboratorium GmbH, Allergan, Deutsche Dermatologische Gesellschaft, Paul-Ehrlich-Gesellschaft für Chemotherapie e.V., Deutsche Radioonkologie e.V.	No	No	Institution: clinical studies (many companies)
3	**Other relationships**	**No**	**No**	**No**	**No**	**No**
		Talme, Toomas	**Thio, Hok Bing**	**van de Kerkhof, Peter**	**Werner, Ricardo**	**Yawalkar, Nikhil**
1	**Work under consideration for these guidelines**					
1.1	Grant	No	No	No	Institution: European Dermatology Forum	No
1.2	Consulting fee or honorarium	No	No	No	No	No
1.3	Support for travel to meetings for the study or other purposes	No	No	No	No	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees and the like	No	No	No	Institution: European Dermatology Forum	No
1.5	Payment for writing or reviewing the manuscript	No	No	No	Institution: European Dermatology Forum	No

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Appendix 4.1 *(Continued)*

		Talme, Toomas	Thio, Hok Bing	van de Kerkhof, Peter	Werner, Ricardo	Yawalkar, Nikhil
1.6	Provision of writing assistance, medicines, equipment or administrative support	No	No	No	No	No
1.7	Other	No	No	No	No	No
2	**Relevant Financial Activities Outside Submitted Work**					
2.1	Board membership	Personally: AbbVie, Novartie, Janssen, Pfizer	No	No	No	No
2.2	Consultancy	No	Personally: Janssen, Novartis, TEVA, Biogen Idec, Abbvie	Institution: Celgene, Centocor, Allmirall, Amgen, Pfizer, Philips, Abbvie, Ely Lilly, Galderma, Novartis, Jansen Cilag, Leo Pharma, Sandoz	No	Personally: Abbvie, Celgene, Essex/MSD, Galderma, Gebro Pharma, Janssen, Leo Pharma, Novartis, Pierre Fabre, Pfizer
2.3	Employment	No	No	No	No	No
2.4	Expert testimony	No	Personally: TEVA	No	No	No
2.5	Grants/grants pending	No	Institution: Pfizer	Institution: Basilea GSK, Pfizer, Ely Lilly, Amgen, Abbvie, Philips Lighting, Jansen Cilag, Leo Pharma, Allmirall	Institution: Stiefel, Intendis	No
2.6	Payment for lectures including service on speakers bureaus	Personally: AbbVie, MSD	Personally: MSD, Janssen, Abbvie	Institution: Celgene, Allmirall, Amgen, Pfizer, Ely Lilly, Abbvie, Galderma, Novartis, Jansen Cilag, Leo Pharma	No	Personally: Abbvie, Celgene, Essex/MSD, Galderma, Gebro Pharma, Janssen, Leo Pharma, Novartis, Pierre Fabre, Pfizer
2.7	Payment for manuscript preparation	No	No	No	No	No
2.8	Patents (planned, pending or issued)	No	No	No	No	No
2.9	Royalties	No	Personally: Elsevier	No	No	No

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Appendix 4.1 *(Continued)*

		Talme, Toomas	Thio, Hok Bing	van de Kerkhof, Peter	Werner, Ricardo	Yawalkar, Nikhil
2.10	Payment for development of educational presentations	No	Personally: Astellas	No	No	Personally: AbbVie, Celegen, Essex/MSD, Galderma, Gebro Pharma, Janssen, Leo Pharma, Novartis, Pierre Fabre, Pfizer
2.11	Stock/stock options	No	No	No	No	No
2.12	Travel, accommodations and meeting expenses unrelated to activities listed	Personally: AbbVie, Janssen, Pfizer	No	Institution: Celgene, Pfizer, Abbvie, Ely Lilly, Galderma, Novartis, Jansen Cilag, Leo Pharma, Sandoz	No	No
2.13	Other (err on the side of full disclosure)	No	No	No	Institution: Galderma Laboratorium GmbH, Allergan, Deutsche Dermatologische Gesellschaft, Paul-Ehrlich-Gesellschaft für Chemotherapie e.V., Deutsche Radioonkologie e.V.	No
3	**Other relationships**	**No**	**No**	**No**	**No**	**No**

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4.2 Electronic search strategies used for the literature search

Medline via OvidSP

ID	Search
1.	exp Psoriasis/
2.	psoriasis.mp.
3.	1 or 2
4.	exp Methotrexate/
5.	'methotrexat*'.ab,ti.
6.	MTX.ab,ti.
7.	exp Cyclosporine/
8.	'c#clospor*'.ab,ti.
9.	CSA.ab,ti.
10.	exp Fumarates/
11.	'fumar*'.ab,ti.
12.	'monomethylfumar*'.ab,ti.
13.	'dimethylfumar*'.ab,ti.
14.	FAE.ab,ti.
15.	DMF.ab,ti.
16.	MMF.ab,ti.
17.	exp Acitretin/
18.	acitretin.ab,ti.
19.	infliximab.ab,ti.
20.	etanercept.ab,ti.
21.	ustekinumab.ab,ti.
22.	adalimumab.ab,ti.
23.	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24.	3 and 23
25.	Randomized Controlled Trials as Topic/
26.	randomized controlled trial/
27.	Random Allocation/
28.	Double-Blind Method/
29.	Single Blind Method/
30.	clinical trial/
31.	clinical trial, phase I.pt.
32.	clinical trial, phase II.pt.
33.	clinical trial, phase III.pt.
34.	clinical trial, phase IV.pt.
35.	controlled clinical trial.pt.
36.	randomized controlled trial.pt.
37.	multicenter study.pt.
38.	clinical trial.pt.
39.	exp Clinical Trials as topic/
40.	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41.	(clinical adj trial$).tw.
42.	((singl$ or doubl$ or treb$ or tribl$) adj (blind$3 or mask$3)).tw.
43.	Placebos/
44.	placebo$.tw.
45.	randomly allocated.tw.

Appendix 4.2 *(Continued)*

ID	Search
46.	(allocated adj2 random$).tw.
47.	41 or 42 or 43 or 44 or 45 or 46
48.	40 or 47
49.	case report.tw.
50.	letter/
51.	historical article/
52.	49 or 50 or 51
53.	48 not 52
54.	24 and 53

Medline In-Process via OvidSP

ID	Search
1.	psoriasis.mp.
2.	'methotrexat*'.ab,ti.
3.	MTX.ab,ti.
4.	'c#clospor*'.ab,ti.
5.	CSA.ab,ti.
6.	'fumar*'.ab,ti.
7.	'monomethylfumar*'.ab,ti.
8.	'dimethylfumar*'.ab,ti.
9.	FAE.ab,ti.
10.	DMF.ab,ti.
11.	MMF.ab,ti.
12.	acitretin.ab,ti.
13.	infliximab.ab,ti.
14.	etanercept.ab,ti.
15.	ustekinumab.ab,ti.
16.	adalimumab.ab,ti.
17.	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18.	1 and 17
19.	Randomized Controlled Trials as Topic/
20.	randomized controlled trial/
21.	Random Allocation/
22.	Double-Blind Method/
23.	Single Blind Method/
24.	clinical trial/
25.	clinical trial, phase I.pt.
26.	clinical trial, phase II.pt.
27.	clinical trial, phase III.pt.
28.	clinical trial, phase IV.pt.
29.	controlled clinical trial.pt.
30.	randomized controlled trial.pt.
31.	multicenter study.pt.
32.	clinical trial.pt.
33.	exp Clinical Trials as topic/
34.	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35.	(clinical adj trial$).tw.
36.	((singl$ or doubl$ or treb$ or tribl$) adj (blind$3 or mask$3)).tw.

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Appendix 4.2 *(Continued)*

ID	Search
37.	Placebos/
38.	placebo$.tw.
39.	randomly allocated.tw.
40.	(allocated adj2 random$).tw.
41.	35 or 36 or 37 or 38 or 39 or 40
42.	34 or 41
43.	case report.tw.
44.	letter/
45.	historical article/
46.	43 or 44 or 45
47.	42 not 46
48.	18 and 47

Embase via OvidSP

ID	Search
1.	exp Psoriasis/
2.	psoriasis.mp.
3.	1 or 2
4.	exp Methotrexate/
5.	'methotrexat*'.ab,ti.
6.	MTX.ab,ti.
7.	exp Cyclosporine/
8.	'c#clospor*'.ab,ti.
9.	CSA.ab,ti.
10.	exp Fumarates/
11.	'fumar*'.ab,ti.
12.	'monomethylfumar*'.ab,ti.
13.	'dimethylfumar*'.ab,ti.
14.	FAE.ab,ti.
15.	DMF.ab,ti.
16.	MMF.ab,ti.
17.	exp Acitretin/
18.	acitretin.ab,ti.
19.	infliximab.ab,ti.
20.	etanercept.ab,ti.
21.	ustekinumab.ab,ti.
22.	adalimumab.ab,ti.
23.	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24.	3 and 23
25.	Clinical trial/
26.	Randomized controlled trial/
27.	Randomization/
28.	Single blind procedure/
29.	Double blind procedure/
30.	Crossover procedure/
31.	Placebo/

Appendix 4.2 *(Continued)*

ID	Search
32.	Randomi?ed controlled trial$.tw.
33.	Rct.tw.
34.	Random allocation.tw.
35.	Randomly allocated.tw.
36.	Allocated randomly.tw.
37.	(allocated adj2 random).tw.
38.	Single blind$.tw.
39.	Double blind$.tw.
40.	((treble or triple) adj blind$).tw.
41.	Placebo$.tw.
42.	Prospective study/
43.	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44.	Case study/
45.	Case report.tw.
46.	Abstract report/or letter/
47.	44 or 45 or 46
48.	43 not 47
49.	24 and 48

Cochrane Central Register of Controlled Trials

ID	Search
#1	MeSH descriptor: [Psoriasis] explode all trees
#2	psoriasis:ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Methotrexate] explode all trees
#5	methotrexat*:ti,ab
#6	MTX:ti,ab
#7	MeSH descriptor: [Cyclosporine] explode all trees
#8	c?clospor*:ti,ab
#9	CSA:ti,ab
#10	MeSH descriptor: [Acitretin] explode all trees
#11	acitretin:ti,ab
#12	MeSH descriptor: [Fumarates] explode all trees
#13	fumar*:ti,ab
#14	(monomethylfumar*):ti,ab
#15	(dimethylfumar*):ti,ab
#16	FAE:ti,ab
#17	DMF:ti,ab
#18	MMF:ti,ab
#19	etanercept:ti,ab
#20	infliximab:ti,ab
#21	ustekinumab:ti,ab
#22	adalimumab:ti,ab
#23	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
#24	#3 and #23

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