Methods Section

The EuroGuiDerm guideline on AE was developed in accordance with the EuroGuiDerm Methods Manual v1.3. For the detailed description of the guideline development process as well as an overview of the evidence referred to, please see the EuroGuiDerm guideline on AE Methods Report and the Evidence Report.

Both are available alongside the guideline document on the EDF website: https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html

Nomination of experts, management of conflicts of interest

The guideline development group comprised 26 experts from twelve countries nominated by EuroGuiDerm national partner societies or the two guideline co-coordinators (AW and CF). All nominations were reviewed and confirmed by the EuroGuiDerm Board of Directors. In addition, three patient representatives participated in the guideline development.

38% of the experts declared personal-financial interests (for details on classification see EuroGuiDerm Methods Manual v1.3.). *These members were neither eligible to take the lead in a respective working group nor for voting on recommendations pertaining to systemic treatment and on the stepped-care plan.*

Development of the guideline and the consensus process

The chapters of the guideline and the recommendations had been developed by the group members, who formed a number of working groups. Each chapter and all recommendations were reviewed, discussed and amended where appropriate by the entire group. All texts and recommendations were voted on with a necessary minimal agreement of >50% during the consensus conferences. AN facilitated all four consensus conferences using a structured consensus technique. Both internal and external review were conducted. Dissemination and implementation plans were developed. For more details, see Methods Report.

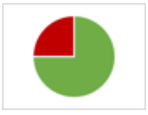
The wording of the recommendations was standardized (as suggested by the GRADE Working Group [1]).

Wording of recommendations

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.
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.
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 reliable evidence data available, conflicting outcomes, etc.)
Weak recommendation	'We suggest against . . .'	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.

against the use of an intervention			
Strong recommendation **against** the use of an intervention	'We recommend against . . .'	↓↓	We believe that all or almost all informed people would make a choice against that intervention.

The recommendation are presented throughout this guideline as displayed below: alongside the wording of the recommendations the arrow(s) and colors indicate the direction and the strength of each recommendation. The rate of agreement (consensus strength) is also displayed as the actual percentage and in form of a category-type pie chart. For all systemic drugs, we added the dosages (according to the European Medical Agency). Additionally, the certainty of evidence was added where applicable (bold – significant difference; Associations are reported in line with Drucker et. al[2]).

We **suggest** using azathioprine in AE patients who are candidates for systemic treatment.	↑	>75%  (14/15) Evidence and consensus based, see Evidence Report

azathioprine: off licence; commonly used dosage
adults: 1-3 mg/kg per day
children: 1-3 mg/kg per day

Certainty of evidence[2, 3]:

Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕⊕○ MODERATE for standardized mean difference **change in signs**

⊕⊕○○ LOW for standardized mean difference QoL, itch

For azathioprine versus other drugs, see Evidence Report

Update 2024

The second update of the guideline was initiated to include lebrikizumab in the guideline. Lebrikizumab was approved by the EMA after the last update of the guideline, which is why there was no recommendation for it in the old guideline. In addition, baricitinib received an extension of approval for use in children and adolescents aged 2 years and older. Furthermore, an update of the network meta-analysis by Drucker et al. was published in September 2024.[3, 4]

The new evidence from the updated network meta-analysis, and the changes prepared by the coordinators and the EuroGuiDerm team in the background text of the chapters on systemic treatment and new versions of the stepped-care plans and drug tables were presented to the GDG and put to the vote in an online survey. In addition, a new recommendation on lebrikizumab and two modified recommendations from the the sections on pregnancy and breastfeeding in which lebrikizumab was added were voted on.

All experts were asked to vote (agree, abstain, reject). Alternative suggestions could be entered as a reply option. Experts could not see how others had voted. Only the EuroGuiDerm team had access to

the results. All authors could participate but the votes of those with personal financial conflicts of interest did not count.

For the update in 2024, the group comprised experts from twelve countries. Ten experts (35,7%) declared personal financial conflicts of interest, see below.

Title	First name	Last name	Personal- financial conflicts of interest
	Bernd	Arents	None
Dr.	Nora	Aszodi	None
Prof. Dr.	Sebastien	Barbarot	S Barbarot is an investigator or speaker for Astrazeneca, Almirall, Sanofi-Genzyme, Abbvie, Galderma, Alexion, Novartis,
Prof. Dr.	Thomas	Bieber	T Bieber has been/currently a consultant for numerous pharmaceutical companies with MP in this indication
Dr.	Helen A.	Brough	None
Prof. Dr.	Piergiacomo	Calzavara Pinton	None
Dr.	Stéphanie	Christen-Zäch	None
Dr.	Mette	Deleuran	Advisor and/or speaker for the following companies:AbbVie, Almirall, Apogee, Eli Lilly, Galderma, Incyte, Kymab, La Roche Posay, Leo Pharma, Medscape, Mustela, Numab, Pfizer, Pierre Fabre, Regeneron, Sanofi, UCB, Union Therapeutics.
Prof. Dr.	Carsten	Flohr	In the past 3 years: Personal payments for educational activities related to atopic eczema, sponsored by Sanofi, Almirall,
Dr.	Nicole	Fosse	None
Dr.	Krisztián	Gáspár	None
Dr.	Louise	Gerbens	None
Prof. Dr.	Uwe	Gieler	None
Prof. Dr.	Giampiero	Girolomoni	Personal fees for speaking at sponsored meetings from Abbvie, Almirall, Bristol Myers Squibb, Pfizer, Eli Lilly, Boerhinge
Prof. Dr.	Stamatis	Gregoriou	None
	Holland	Suzi	None
Prof. Dr.	Charlotte	Mortz	None
MD PhD	Uffe	Nygaard	None
MD PhD	Eva Maria	Rehbinder	None
Prof. Dr. Dr.	Johannes	Ring	Honoraria for lectures and consulting for the following companies:AbbVie, Sanofi, Allergika, Pfizer, Viatris

Dr.	Mariateresa	Rossi	None
Dr.	Esther	Serra-Baldrich	None
Prof. Dr.	Dagmar	Simon	None
Prof. Dr.	Zsuzsanna	Szalai	None
Prof. Dr.	Jacek C.	Szepietowski	Advisory Board Member of Galderma, Leo Pharma, Novartis, Sanofi-Genzyme, Pfizer and UCB. Speaker for Abbvie, Almirall, Janssen-Cilag, Eli-Lilly, Leo-Pharma, Pfizer, Sanofi-Genzyme, UCB. Investigator for Abbvie, BMS, Galderma, Incyte, Pfizer, UCB, Regeneron
Dr.	Antonio	Torrelo	"Viatris - Advisory boards, lecturing Pierre Fabre - Lecturing Sanofi - Lecturing Eli Lilly - Advisory boards, lecturing"
Prof. Dr.	Thomas	Werfel	T Werfel has performed consultancies for Abbvie, Almirall, Galderma, LEO, Lilly, Novartis, Pfizer, Sanofi-Regeneron and has lectured at educational events sponsored by Abbvie, Almirall, Galderma, LEO Pharma, Lilly, Pfizer, Sanofi and Novartis
Prof. Dr. med. Dr. h.c.	Andreas	Wollenberg	A Wollenberg has received grants, personal fees or nonfinancial support from AbbVie, Almirall, Amgen, Beiersdorf, Bioderma, Bioproject, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, DKSH, Eli Lilly, Galderma, Glenmark, GSK, Hans Karrer, Hexal, Janssen-Cilag, Kyowa Kirin, Leo Pharma, L'Oreal, Maruho, MedImmune, Merck, MSD, Mylan, Novartis, Pfizer, Pierre Fabre, Regeneron, Sandoz, Santen, Sanofi-Aventis and UCB.

The updated guideline document (chapter 7-10.3 and chapter 17, the stepped-care plans and the drug tables) the Evidence Report and the Methods Report were send to: EDF Board, all supporting societies and pharmaceutical companies for external review. After the review phase all comments from the reviewer were combined in an word documents. Editorial comments were resolved by the EuroGuiDerm Team. All other comments were sent to the clinical coordinators AW and CF to be resolved. All changes to the guideline were made using the "track changes" function. All reviewers received feedback to their comments and all changes resulting from the commenting phase are clearly visible. An anonymised version of all comments, feedback and action taken are available from euroguiderm@debm.de

Evidence

The living systematic review by Drucker and colleagues[3, 4] was used as the evidence base based on which we created an evidence-to-decision framework (see Evidence Report). Furthermore, challenges exist with comparing clinical trials in AE due to their differences in trial design, including study comparators, rules for rescue treatment, washout periods for topical and systemic treatments, inclusion criteria, and the duration of the screening period.[5] Finally, this analysis does not take into consideration the overall management plan that targets long-term stabilization, flare prevention and avoidance of side-effects beyond 16 weeks[6]. We only summarize the results here. For limitations please refer to the website.

For each recommendations that is evidence-based, we added the certainty of the evidence when compared to placebo[2]. The assessment of the certainty of evidence leads to four grades, see Figure 1 (Table 5.1. GRADE Handbook[7]).

High ⊕⊕⊕⊕: we are **very confident** that the true effect lies close to that of the estimate of the effect.
Medium ⊕⊕⊕◯: 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.
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.

Figure 1 Definitions of "certainty of evidence" [7]

Excerpt from the publication of the network meta-analysis 'Systemic Systemic Immunomodulatory Treatments for Atopic Dermatitis: Living Systematic Review and Network Meta-Analysis Update ' by Aaron M. Drucker and colleagues, Sep 2024.[4]

„[…] Compared to dupilumab (600 mg followed by 300 mg every 2 weeks), lebrikizumab (500 mg at weeks 0 and 2 followed by 250 mg every 2 weeks) was probably associated with no important difference in reductions in EASI (MD, −2.0; 95% CrI, −4.5 to 0.3; moderate certainty), POEM (MD, −1.1; 95% CrI, −2.5 to 0.2; moderate certainty), DLQI (MD −0.2; 95% CrI, −2.1 to 1.6; moderate certainty) scores, and was associated with no important difference in reduction in PP-NRS (MD 0.1; 95% CrI, −0.4 to 0.6; high certainty) scores in trials up to 16 weeks—positive numbers indicate more improvement with lebrikizumab. […] Dupilumab was associated with higher odds than lebrikizumab of achieving EASI-50 (OR, 1.4; 95% CrI, 1.0 to 2.0), EASI-75 (OR, 1.4; 95% CrI, 1.0 to 1.9), EASI-90 (OR, 1.5; 95% CrI, 1.1 to 2.2), and IGA success (OR, 1.3; 95% CrI, 0.9 to 1.9). […] The relative efficacy of other approved systemic medications was similar to that found by previous NMA updates, with high-dose upadacitinib and abrocitinib demonstrating numerically highest relative efficacy. Results of efficacy analyses using standardized mean differences to compare newer to older medications (eg, methotrexate) and results of safety comparisons (serious adverse events, withdrawals due to adverse events) remain imprecise, with wide CrIs. […] page 938, Drucker et al. 2024.[4]

Linking evidence to recommendations

In the table below, we link the evidence from the NMA directly to the recommendations made. For additional information and justifications, please see the corresponding chapters.

Recommendation	**Short term (8-16 weeks) vs placebo** Bold = statistically significant difference
We suggest azathioprine in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2022[2, 3]: ⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs** -0.6 (-1, -0.2) ⊕⊕◯◯ LOW for standardized mean difference QoL -0.4 (-0.9, 0.1), itch -0.6 (-1.2, 0)
We recommend ciclosporin to achieve disease control in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2022[2, 3]: Higher dose ⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs** -1 (-1.6, -0.4) ⊕⊕⊕◯ MODERATE for standardized mean difference **QoL** -0.7 (-1.3, -0.1) ⊕⊕◯◯ LOW for standardized mean difference itch -0.7 (-1.5, 0.2) Lower dose ⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs** -0.7 (-1.4, -0.1)

	⊕⊕◯◯ LOW for standardized mean difference QoL -0.5 (-1.1, 0.2) ⊕⊕◯◯ LOW for standardized mean difference itch -0.7 (-1.6, 0.3)
We suggest methotrexate in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2022[2, 3]: ⊕⊕◯◯ LOW for standardized mean difference change in signs -0.6 (-1, -0.2), QoI -0.4 (-0.9, 0.1), itch -0.6 (-1.2, 0)
We recommend dupilumab in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2024[3, 4]: ⊕⊕⊕⊕ HIGH for mean difference **EASI** -10.5 (-11.9, -9.2); **POEM** -7.3 (-8, -6.7); **peak pruritus NRS** -2.1 (-2.3, -1.8); **DLQI** (-4.9 (-5.4, -4.3)
We recommend lebrikizumab in AE patients, who are candidates for systemic treatment.	Network meta-analysis from 2024[3, 4]: ⊕⊕⊕⊕ HIGH for mean difference **POEM** -6.2 (-7.4, -5.1) ⊕⊕⊕◯ MODERATE for mean difference **EASI** -8.5 (-10.4, -6.5); **DLQI** -4.7 (-6.4, -2.8) ⊕⊕◯◯ LOW for mean difference **peak pruritus NRS** -2.1 (-2.6, -1.7)
We recommend tralokinumab in AE patients, who are candidates for systemic treatment.	Network meta-analysis from 2024[3, 4]: ⊕⊕⊕⊕ HIGH for mean difference **POEM** -4.2 (-5, -3.4) ⊕⊕⊕◯ MODERATE for mean difference **peak pruritus NRS** -1 (-1.2, -0.7); **DLQI** -2.4 (-3.1, -1.6) ⊕⊕◯◯ LOW for mean difference **EASI** -6.2 (-7.8, -4.7)
We recommend abrocitinib in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2024[3, 4]: 100 mg ⊕⊕⊕⊕ HIGH for mean difference **EASI** -8.5 (-10.3, -6.7); **POEM** -5.1 (-6.1, -4.1) ⊕⊕⊕◯ MODERATE for mean difference **peak pruritus NRS** -1.6 (-2.1, -1.1); **DLQI** -3.4 (-4.3, -2.6) 200 mg ⊕⊕⊕⊕ HIGH for mean difference **EASI** -12.8 (-14.6, -11.1); **POEM** -8.4 (-9.3, -7.5); **DLQI** -5.6 (-6.3, -4.8) ⊕⊕⊕◯ MODERATE for mean difference **peak pruritus NRS** -2.4 (-3, -1.8)
We recommend baricitinib in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2024[3, 4]: 2 mg ⊕⊕⊕◯ MODERATE for mean difference **EASI** -5.1 (-6.9, -3.4); **POEM** -3.8 (-4.9, -2.7); **peak pruritus NRS -1**.2 (-1.6, -0.9); **DLQI** -2.3 (-3.1, -1.4) 4 mg ⊕⊕⊕⊕ HIGH for mean difference **POEM** -5.4 (-6.6, -4.2); **peak pruritus NRS** -1.6 (-2, -1.3) ⊕⊕⊕◯ MODERATE for mean difference **EASI** -7.5 (-9.4, -5.6); **DLQI** -3.5 (-4.4, -2.6)
We recommend upadacitinib in AE patients who are candidates for systemic treatment	Network meta-analysis from 2024[3, 4]: 15 mg ⊕⊕⊕⊕ HIGH for mean difference **EASI** -11 (-12.6, -9.4) ⊕⊕⊕◯ MODERATE for mean difference **POEM** -7 (-11.2, -2.9); **peak pruritus NRS** -2.4 (-2.8, -2) 30 mg ⊕⊕⊕⊕ HIGH for mean difference **EASI** -13.5 (-15.2, -11.9); **POEM** -10.7 (-14.8, -6.5); **peak pruritus NRS** -3.3 (-3.6, -3.1)
AE = atopic eczema; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; NMA = network meta analysis; OR = Odds ratio; POEM = Patient-Oriented Eczema Measure; PPNRS = Peak Pruritus Numerical Rating Scale; RoB = Risk of Bias; VAS = visual analog scale	

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