Received: 10 July 2023 | Accepted: 27 July 2023

DOI: 10.1111/ddg.15229

GUIDELINE

S3 guideline Atopic dermatitis: Part 2 - Systemic treatment

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Summary
The present S3 guideline was created based on the European English-language S3 guideline, with special consideration given to the medical conditions in the German-speaking region, and with additions from the previous German-language version, in accordance with the criteria of the AWMF. This second part of the guideline addresses the systemic therapy of atopic dermatitis (AD). It covers topics such as the indication for systemic therapy in children, adolescents, and adult patients with AD. Furthermore, it addresses all medications approved for AD, such as the biologics dupilumab and tralokinumab, the Janus kinase inhibitors abrocitinib, baricitinib, and upadacitinib, as well as conventional immunosuppressive therapies with systemic glucocorticosteroids and ciclosporin. Additionally, it discusses systemic off-label therapies. The first part of the guideline, published separately, includes the definition and diagnostic aspects of AD, describes topical therapy, non-drug therapy approaches, and addresses aspects related to special patient groups.

AWMF registry number: 013–027
Validity of Guideline: The present guideline is valid until June 15, 2028
Participating societies:
DDG – German Dermatological Society e.V.
BVDD – Professional Association of German Dermatologists e.V.
ÖGDV – Austrian Society of Dermatology and Venereology
SGDV – Swiss Society of Dermatology and Venereology
DGAKI – German Society for Allergology and Clinical Immunology e.V.
DGKJ – German Society for Pediatric and Adolescent Medicine e.V.
BVKJ – Professional Association of Pediatricians and Adolescent Medicine e.V.
GPA – Society for Pediatric Allergology and Environmental Medicine e.V.
DGPM – German Society for Psychosomatic Medicine and Medical Psychotherapy e.V.
German Network for Health Services Research e.V.
German Allergy and Asthma Association e.V.
DGpRP – German Society for Pediatric Rehabilitation and Prevention e.V.
AGNES – Working Group for Atopic Dermatitis Education e.V.
German Atopic Dermatitis Association e.V.
German Contact Allergy Group e.V.
Working Group Allergology of the German Dermatological Society
Working Group Health Economics and Evidence-Based Medicine of the German Dermatological Society
Working Group Occupational and Environmental Dermatology of the German Dermatological Society
Working Group Pediatric Dermatology of the German Dermatological Society
Working Group Allergology of the Swiss Society for Dermatology and Venereology

INTRODUCTION

The present guideline is an update of the AWMF S2k guideline "Diagnosis and treatment of atopic dermatitis" published in 2015. The update was made by adaptation of the "EUROGUIDERM GUIDELINE ON ATOPIC ECZEMA" of Wollenberg A et al. that is published in its final form under https://doi.org/10.1111/jdv.18345 and https://doi.org/10.1111/jdv.18429. Several sections of the guideline have been adopted without changes from the previous versions.

The present guideline consists of two sections, published separately: part 2 (this publication) addresses the systemic therapy of atopic dermatitis, part 1 is focused on the general aspects of atopic dermatitis, local therapy, non-pharmacological therapeutic approaches, and special aspects in certain patient groups.

In both published sections, the recommendations are complete and unabridged while the content on medical background and available studies is presented in a shortened form. The unabridged long version of the guideline is available on the AWMF website (https://register.awmf.org/de/leitlinien/detail/013-027).

INTRODUCTION TO SYSTEMIC THERAPY

In manifest inflammatory lesions, systemic therapy *shall* be combined with a topical anti-inflammatory treatment.	↑↑	100% consensus-based

A systemic therapy is indicated, if the disease cannot be controlled adequately with topical treatments – and in adults, possibly not even with UV therapy. In addition, a systemic therapy may be useful to reduce the total amount of topical glucocorticosteroids (TCS) in patients with AD requiring large quantities of potent TCS over prolonged periods.

In principle, either patients with a high total score (scale definition), patients not responding clinically to correctly performed topical or exhausted therapy with ultraviolet (UV) light (functional definition), or patients unable to participate in activities of daily life despite adequate treatment regimen (social definition) are suitable for a systemic therapy.

In clinics and offices, the indication for systemic therapy and the response of patients to topical and systemic treatments shall be recorded and documented in appropriate form. The indication for systemic therapy in AD should be documented in a standardized manner. A checklist for the indication of systemic therapy in AD for adult patients is presented in Figure 1. Analogous checklists for the age groups of children and adolescents are available on the AWMF website.

The objective signs can be assessed by clinical severity scores, such as *objective SCORing Atopic Dermatitis* (oSCORAD) or *Eczema Area and Severity Index* (EASI), the subjective symptoms, for example, by the *Patient Oriented Eczema Measure* (POEM). An appropriate *composite score* like SCORAD (*SCORing Atopic Dermatitis*) will assess signs and symptoms at the same time. The barrier function can be determined objectively by means of a skin function measurement device via determination of transepidermal water loss (TEWL) and hydration of the stratum corneum (SC). Depending on age, the *Dermatology Life Quality Index* (DLQI) or the *Children's Dermatology Life Quality Index* (CDLQI) can be used for assessing the quality of life. The *Patient-Oriented SCORAD* (PO-SCORAD) can be used to determine the severity over time under real-life conditions. It must be considered that the indication for systemic treatment is a decision to be made individually for each patient.

Prior to initiation of a systemic treatment, it is important to exclude relevant differential diagnoses, such as cutaneous T-cell lymphomas and, in individual cases, primary immunodeficiency syndromes, potential provocation factors like allergens, as well as behavior- and *compliance*-related reasons for a poor response.[1]

In recent years, numerous new substances have been approved for AD, and others are in the last phase of clinical development. The approval programs for the various new biologics and low-molecular agents offer considerably higher levels of evidence than is the case for longer-established drugs and phototherapy.

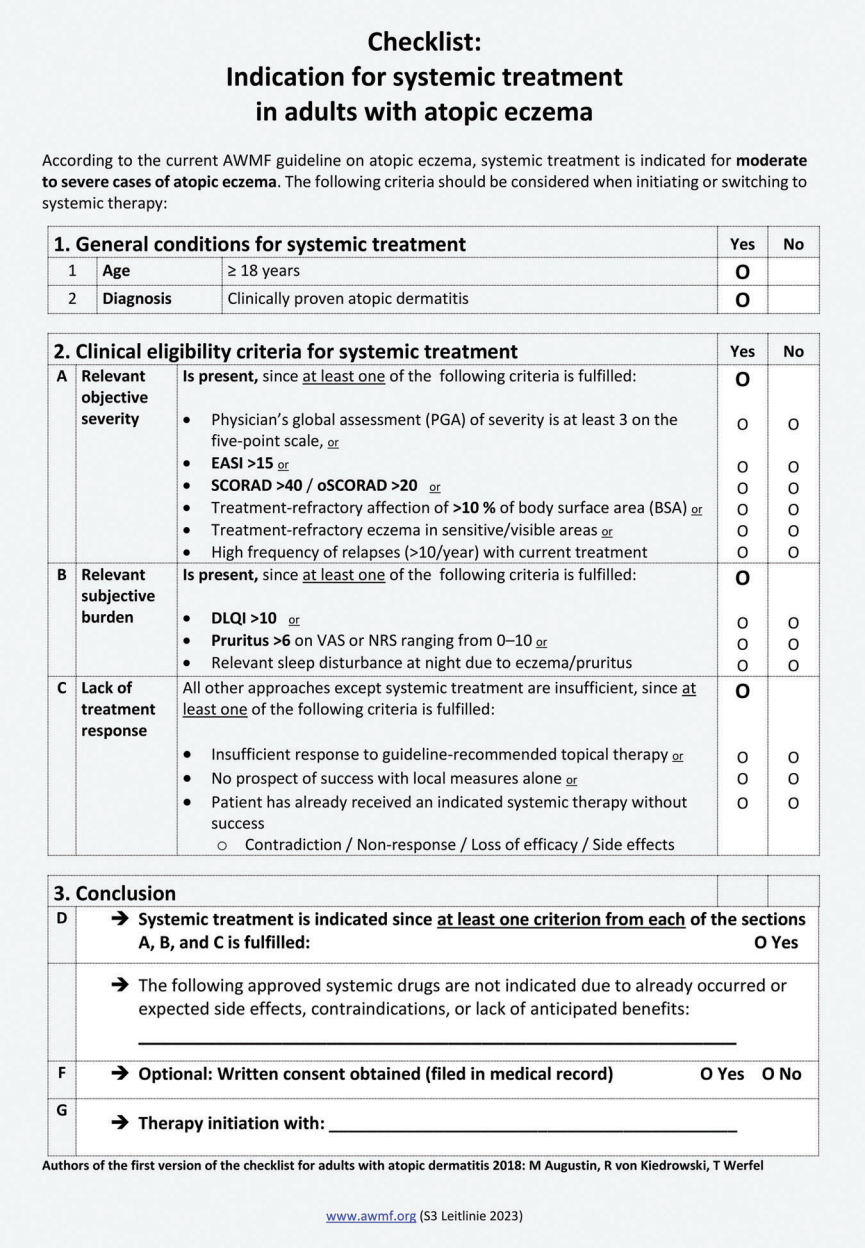
In the past, rather conventional immunosuppressants with a broad effect, such as systemic glucocorticosteroids, ciclosporin, azathioprine, mycophenolate mofetil, gastro-resistant mycophenolate sodium, and methotrexate, have been used for the systemic therapy of AD. Except for systemic glucocorticosteroids and ciclosporin, these substances are not approved for the indication of AD. Similar to the new Janus kinase inhibitors baricitinib, abrocitinib, and upadacitinib, ciclosporin and systemic glucocorticosteroids have a rapid onset of effect, while the other conventional immunosuppressants and the newer antibodies dupilumab und tralokinumab directed against T helper 2 (Th2) cells require several weeks before they are fully effective.

Systemic therapy in childhood

Specific aspects of AD in childhood and adolescence, as well as the management of the disease in these populations are also addressed in part 1 of these guidelines.

In childhood and adolescence, an immunomodulatory systemic therapy shall also be considered for moderate to severe disease courses, if AD results in significant somatic and/or psychosocial impairment and cannot be treated adequately despite exploiting the available local therapeutics. The indication for systemic therapy should be

FIGURE 1 Checklist: Indication for systemic treatment of atopic dermatitis in adults.



Checklist: Indication for systemic treatment in adults with atopic eczema

According to the current AWMF guideline on atopic eczema, systemic treatment is indicated for **moderate to severe cases of atopic eczema**. The following criteria should be considered when initiating or switching to systemic therapy:

1. General conditions for systemic treatment			**Yes**	**No**
1	**Age**	≥ 18 years	**O**	
2	**Diagnosis**	Clinically proven atopic dermatitis	**O**	

2. Clinical eligibility criteria for systemic treatment			**Yes**	**No**
A	**Relevant objective severity**	**Is present,** since at least one of the following criteria is fulfilled:	**O**	
		• Physician's global assessment (PGA) of severity is at least 3 on the five-point scale, or	O	O
		• **EASI >15** or	O	O
		• **SCORAD >40 / oSCORAD >20** or	O	O
		• Treatment-refractory affection of **>10 %** of body surface area (BSA) or	O	O
		• Treatment-refractory eczema in sensitive/visible areas or	O	O
		• High frequency of relapses (>10/year) with current treatment	O	O
B	**Relevant subjective burden**	**Is present,** since at least one of the following criteria is fulfilled:	**O**	
		• **DLQI >10** or	O	O
		• **Pruritus >6** on VAS or NRS ranging from 0–10 or	O	O
		• Relevant sleep disturbance at night due to eczema/pruritus	O	O
C	**Lack of treatment response**	All other approaches except systemic treatment are insufficient, since at least one of the following criteria is fulfilled:	**O**	
		• Insufficient response to guideline-recommended topical therapy or	O	O
		• No prospect of success with local measures alone or	O	O
		• Patient has already received an indicated systemic therapy without success	O	O
		○ Contradiction / Non-response / Loss of efficacy / Side effects		

3. Conclusion		
D	➔ **Systemic treatment is indicated since at least one criterion from each of the sections A, B, and C is fulfilled:**	**O Yes**
	➔ The following approved systemic drugs are not indicated due to already occurred or expected side effects, contraindications, or lack of anticipated benefits: _____	
F	➔ **Optional: Written consent obtained (filed in medical record)**	**O Yes O No**
G	➔ **Therapy initiation with:** _____	

Authors of the first version of the checklist for adults with atopic dermatitis 2018: M Augustin, R von Kiedrowski, T Werfel

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carefully verified and documented especially in children and adolescents by means of a checklist (see AWMF website). Prior to therapy start, parents and – if appropriate due to age – the affected child should be informed in detail and in a generally understandable manner about potential benefits, possible risks, administration mode, and, if necessary, required follow-up examinations. If subcutaneous injections are required, training should be provided in an age-appropriate form for the respective method of administration.

The following recommendations for systemic agents are based on the efficacy and safety data of the *Living Network Meta-analysis* of Drucker et al.,[2] other published literature, and the expertise of the guideline group.

APPROVED DRUGS

Short-term intervention with systemic glucocorticosteroids

Systemic glucocorticosteroids *should* be used in patients with AD *exclusively* as short-term therapy (rescue therapy) in acute flares for a maximum of 3 weeks.	↑	100% consensus-based
Long-term treatment with systemic glucocorticosteroids *shall not* be performed in patients with AD.	↓↓	100% consensus-based

Modes of action and efficacy

Glucocorticosteroids comprise a group of steroid hormones that bind to the glucocorticoid receptor. The activated glucocorticoid receptor complex upregulates the expression of anti-inflammatory proteins and suppresses the expression of proinflammatory proteins resulting in a broad anti-inflammatory effect.[3]

Despite the regular use of systemic glucocorticosteroids in clinical practice, there are very few studies on adult and pediatric patients with AD. In studies on children and adults, systemic glucocorticosteroids did not achieve long-term remission. The efficacy of systemic glucocorticosteroids is markedly lower than that of ciclosporin.[4,5]

Dosage: flare, short-term treatment, long-term treatment

- Acute flare: the starting dose is usually 0.5 mg/kg/day in adults and considerably lower in children, with 0.2 mg/kg/day. The treatment should be discontinued or reduced as soon as possible.
- As with any systemic treatment of patients with AD, the therapy with systemic glucocorticosteroids shall be combined with emollients and a topical anti-inflammatory therapy, if needed.

Safety

In the context of short-term use, systemic glucocorticosteroids have a broad therapeutic index. The toxicity is dependent on mean dose, cumulative dose, and duration of administration. The major side effects of high doses and long-term use (usually, > 0.5 mg/kg/day or > 0.2 mg/kg/day in children) include skin atrophy, increase in weight, sleep problems, mood changes, hyperglycemia or emerging diabetes, gastric ulcer/gastritis, osteoporosis, and increased susceptibility to infection.[6] Especially in case of long-term use, patients may also develop adrenal suppression, while discontinuation of the treatment is sometimes challenging due to the associated risk of rapid recurrence or rebound phenomena during gradual dose reduction. Accordingly, long-term therapy with systemic glucocorticosteroids should be avoided in adults and children. Even a relatively high dose can simply be discontinued during the first five treatment days, and discontinuation without side effects has been described even after up to three weeks of treatment.[7]

Monitoring

While no standard variables are recommended for the acute *rescue* therapy, monitoring activities may be required (such as, blood glucose determination in diabetics and risk patients) depending on the needs of the individual patient.

Combination with other therapies

During therapy with systemic glucocorticosteroids, there is no contraindication for other AD treatments. A combination of systemic glucocorticosteroids with UV light is also possible in adults.

Specific information

The treatment of acute AD flares with oral glucocorticosteroids is moderately effective.[4,5]

Systemic glucocorticosteroids have an unfavorable benefit-risk relation concerning long-term treatment of AD in adults and children. Therefore, such a long-term treatment (> 3 weeks) shall not be performed.

Interval therapy with ciclosporin

Ciclosporin *may be considered* as an interval therapy for disease control in adult patients with AD who are candidates for systemic treatment.	0	100% evidence– and consensus-based, see evidence report
If using ciclosporin for the indication AD, the ratio of expected benefits to risks *shall* be individually assessed against the background of therapeutic alternatives.	↑↑	100% consensus-based
Ciclosporin *shall not* be used in combination with UV therapies.	↓↓	100% consensus-based
Initially, higher ciclosporin dosages (up to 5 mg/kg [body weight] BW) *shall* be used to achieve a rapid response.	↑↑	100% consensus-based
If there is a good response, the therapy *shall* be interrupted after 4–6 months.	↑↑	100% consensus-based
In AD with severe disease course, a therapy over a longer period than 6 months *may be considered* (if well tolerated).	0	
Close monitoring of blood pressure and renal function parameters *shall* be performed in patients with AD treated with ciclosporin.	↑↑	100% consensus-based

Modes of action and efficacy

Ciclosporin inhibits the activation and proliferation of T cells by blocking the production of cytokines depending on the transcription factor NFAT (*nuclear factor of activated T cells*).

Ciclosporin is approved as first-line therapy for patients aged 16 years and above with severe disease. Ciclosporin is

highly effective against AD in both children and adults, and it is better tolerated by children.[5,8] In head-to-head-studies, ciclosporin was superior to methotrexate, prednisolone, intravenous immunoglobulins (IVIG), UVA, and UVB, and was similarly effective as gastro-resistant mycophenolate sodium.[9,10] In short-term treatment of AD, higher doses of ciclosporin (5 mg/kg daily) result in a more rapid response and are more effective than lower doses (2.5–3 mg/kg daily).[9] The long-term use of ciclosporin for up to one year may be considered in exceptional cases with close safety monitoring. This is based on several studies that are, however, of limited validity with respect to efficacy due to their open design and the high dropout rate.[9] Given the availability of newer and better therapeutic alternatives, therapies exceeding the duration of one year are no longer recommended even if ciclosporin is well tolerated. For the treatment of older patients with AD aged 65 years and above, well-documented experience for treatment with ciclosporin is limited.

Use and dosage in AD: acute flare, short-term treatment, long-term treatment

- Approved from an age ≥ 16 years
- Standard dose adults: 2.5–5 mg/kg daily in two divided doses
  - Acute flare, short-term treatment: 4–5 mg/kg BW daily
  - Long-term treatment: 2.5–3 mg/kg BW daily
- *Off-label* treatment in children! Dosage children: 2.5–5 mg/kg BW daily in two divided doses
  - As with any systemic treatment of patients with AD, we recommend to combine ciclosporin with emollients and a topical anti-inflammatory therapy, if needed.
  - In children and adolescents < 16 years of age, ciclosporin shall only be used in case of contraindication or lack of efficacy of approved systemic therapies.

Safety

Ciclosporin has a narrow therapeutic index and requires close monitoring of blood pressure and signs of renal failure. Given the potential risk of malignant skin disease, patients on treatment with ciclosporin must be informed that excessive sun exposure without appropriate protection must be avoided. Concomitant UV treatment is contraindicated. Similarly, patients that have already received several cycles of UV therapy should not be treated with ciclosporin.

Monitoring

Dose adjustments may be required on therapy.

- In case of a creatinine increase by > 30% compared to baseline, a dose reduction by 25%, and
- in case of arterial hypertension, a dose reduction or a therapeutic approach with calcium antagonists is possible.

Onset of effect: an onset of effect may be expected after approximately 4 to 8 weeks.

- If no effect has occurred after 6 months, and the maximum dose has been used for 3 months, further treatment should be discontinued.
  - Monitoring program during therapy:
- in the first 2 months, every 1 to 2 weeks
- thereafter, every 4 weeks.
  - Consultation and clinical examination: hypertrichosis, gingival hyperplasia, blood pressure control, tremor, paresthesia, gastrointestinal symptoms.
  - Laboratory analysis: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood count including thrombocytes, alkaline phosphatase, glutamate-pyruvate transaminase (GPT), creatinine, potassium, urine test strip.

Combination with other therapies

Concomitant to ciclosporin, a topical therapy with glucocorticosteroids and/or calcineurin inhibitors may be performed.

Given the potentially increased risk for the development of skin cancer, ciclosporin must not be used in combination with UV light (UVA, UVB, PUVA).

Specific information

Data from studies on the use of ciclosporin in children and adolescents are limited and also have methodical limitations. While the few available studies indicated a relatively good efficacy and tolerance, they do not allow for a final assessment.[5,11] However, given that ciclosporin is used *off-label* in children and adolescents aged < 16 years and in view of its narrow therapeutic index, approved systemic therapeutics with a broader therapeutic index shall be used first (dupilumab, tralokinumab, abrocitinib, baricitinib, upadacitinib).

Ciclosporin may be considered in pregnant women with severe AD. To date, no increased risk of congenital malformations or fetal loss compared to the average population has been identified. An increased risk of a lower birth weight cannot be excluded.[12] If a longer systemic therapy during pregnancy is likely to be required, ciclosporin is the therapy of first choice (*European Task Force on Atopic Dermatitis* [ETFAD] recommendation).[12]

Interval or long-term therapy with biologics

Dupilumab

Dupilumab *shall* be used in children and adults with moderate to severe AD who are candidates for systemic treatment.	↑↑	100% evidence- and consensus-based, see evidence report
Dupilumab *shall* be used as long-term therapy in AD.	↑↑	100% consensus-based
Dupilumab *shall* be used especially in patients with AD who are candidates for systemic treatment and coexisting bronchial asthma, coexisting chronic rhinosinusitis with nasal polyps, coexisting prurigo nodularis, or coexisting eosinophilic esophagitis.	↑↑	100% consensus-based

Modes of action and efficacy

Dupilumab is a fully human monoclonal IgG4 antibody (mAb) approved for the treatment of AD. In Germany, it is available for the treatment of adults since end of 2017. Currently, it is also approved for adolescents and children aged 6 months and above, the approval process for infants from the age of 6 months and children up to the age of 6 years was completed shortly before the guideline was finalised. Dupilumab binds to the α-subunit of the interleukin (IL) 4 receptor that is part of both the IL-4 and the IL-13 receptor complex. The safety and efficacy of dupilumab has been established primarily in placebo-controlled trials with moderate to severe AD.[13] Dupilumab showed significant clinical effects in the evaluation of severity assessed by means of *Eczema Area and Severity Index* (EASI), *Investigator's Global Assessment* (IGA), and *SCORing Atopic Dermatitis* (SCORAD). Moreover, the treatment with dupilumab resulted in a pronounced reduction of pruritus. Dupilumab has proven its efficacy in both intrinsic and extrinsic AD.[14] In addition, dupilumab is approved for the treatment of prurigo nodularis, moderate to severe asthma, eosinophilic esophagitis, and chronic rhinosinusitis with nasal polyps, thus covering several Th2-mediated inflammatory diseases.

Dosage: flare, short-term treatment, long-term treatment

The approved dosage of dupilumab in adults consists of a subcutaneous starting dose of 600 mg, followed by maintenance doses of 300 mg every 2 weeks (Q2W).

For children (6–17 years), the following dose regimens are used: approval from 6 months of age, aged 6–11 years: between 15 und 60 kg body weight, initially 300 mg SC on day 1, followed by another 300 mg SC on day 15, then 300 mg every 4 weeks; from 60 kg and above, 600 mg (two injections of 300 mg each) on day 1, followed by 300 mg every 2 weeks. Aged 12–17: below 60 kg body weight, initially 400 mg SC on day 1 followed by 200 mg every 2 weeks; above 60 kg, initially 600 mg SC followed by 300 mg every 2 weeks.

For children aged 6 months to 5 years, the following dose regimens adapted to weight are used: 5 kg to < 15 kg 200 mg SC every 4 weeks. For children with a body weight of 15 kg to < 30 kg, 300 mg SC every 4 weeks.

Dupilumab has been used in an open-label study for up to 3 years in adults with moderate to severe AD, though several former subjects used the medication in open-label mode for significantly longer. The safety data were consistent with the previously reported studies and the known safety profile of dupilumab.[15]

Safety

Given that the treatment with dupilumab is generally well tolerated, routinely performed blood tests are not recommended.[16] However, a considerable number of patients develops conjunctivitis (up to 20% depending on the study), usually with mild to moderate symptoms.[16,17] In clinical trials, the risk was 2.64-times higher compared to placebo, and in *real-life* studies it amounted to 13% on average.[18] Usually, topical treatment with eyedrops (artificial tears, topical antihistamines, temporarily topical steroids, topical ciclosporin in refractory cases) is sufficient, without the need to discontinue the medication. In refractory cases of severe conjunctivitis, ophthalmologic co-supervision is recommended.[19]

Moreover, local reactions at the injection site have been described more often compared to placebo injections in controlled approval studies. In daily clinical practice these are, however, inconspicuous and of little relevance.

Transient, clinically innocuous increases in eosinophils are quite common with dupilumab. In adults treated with dupilumab for respiratory indications, clinically relevant eosinophilia was described in rare cases (in 7/4,666 patients, six of these with eosinophilic granulomatosis with polyangiitis).[20,21] Therefore, a threshold of 1,500 eosinophilic granulocytes (eos)/μl at indication for treatment with this antibody has been proposed for adults with respiratory indications.[21,22] In adult patients with AD, especially those with additional respiratory disease, it may, therefore, be useful to determine the eosinophils in blood prior to therapy start and to monitor patients with initial counts of > 1,500/μl by laboratory and clinical tests during follow-up.

In individual patients with AD, first manifestation or exacerbation or recurrence of diseases, such as psoriasis

vulgaris and rheumatoid arthritis or Crohn's disease, has been observed on dupilumab therapy, diseases characterized by the important role of IL-17-producing immune cells in the pathogenesis. Accordingly, patients with respective comorbidity on dupilumab therapy should be regularly consulted and clinically examined with respect to recurrence of symptoms and severity of the mentioned diseases.

Monitoring

According to the current summary of product characteristics, no laboratory or instrumental examinations are required for monitoring the therapy.

Combination with other therapies

In a phase III trial, treatment with dupilumab and an accompanying TCS was compared to placebo and an accompanying TCS over a period of 52 weeks.[23] The primary endpoints, including an IGA score of 0 or 1 and EASI-75, were assessed in week 16: more patients receiving dupilumab plus TCS reached the primary endpoints of IGA 0/1 and EASI-75. The results were similar after 52 weeks. In this trial, approximately 15% more of the subjects achieved a 75% reduction of the EASI score after 16 weeks compared to earlier phase III trials, where dupilumab was administered as monotherapy.[13]

Combination therapy with TCS, TCI, and UV light is feasible.

Use in infants > 6 months of age and children < 6 years of age

Since March 21, 2023, dupilumab has been approved by the European Commission for the treatment of children with severe AD at the age of 6 months to 5 years.

In a phase III trial, the efficacy and safety of dupilumab was studied at doses adapted to the body weight (BW ≥ 5 kg to < 15 kg: 200 mg; BW ≥ 15 kg to < 30 kg: 300 mg) with concomitant administration of low-potent TCS in children aged from 6 months to 6 years with moderate to severe AD.[24] In week 16, significantly more patients in the dupilumab group compared to the placebo group had an IGA of 0–1 (28% vs. 4%; $p < 0.0001$) and EASI-75 (53% vs. 11%, $p < 0.0001$). In this age group, conjunctivitis was again more common in the dupilumab group than in the placebo group (5% vs. 0%). No dupilumab-related adverse events were severe or resulted in discontinuation of treatment.

Specific information

In patients with AD with Th2 comorbidity, such as asthma, allergic rhinoconjunctivitis with nasal polyps and/or eosinophilic esophagitis, dupilumab treatment may have positive effects on these diseases, as well.

Tralokinumab

Tralokinumab *shall* be used in children aged 12 years and above and in adult patients with moderate to severe AD who are candidates for systemic treatment.	↑↑	100% evidence- and consensus-based, see evidence report
If there is a response to treatment after 16 weeks, the dose frequency of tralokinumab *shall* be reduced from once every 14 days to once every 28 days. Later, the dose frequency (once every 14 or 28 days) *shall* be adapted to the clinical manifestation.	↑↑	100% consensus-based
Tralokinumab *shall* be used as long-term therapy in AD.	↑↑	100% consensus-based

Modes of action and efficacy

Tralokinumab is a fully human IgG4 mAb neutralizing IL-13; it was approved by the *European Medicines Agency* (EMA) in summer 2021. In two 52-week, double-blind, placebo-controlled phase III trials, adults with moderate to severe AD were randomized and treated with subcutaneously administered tralokinumab 300 mg every 2 weeks or placebo.[25] The tralokinumab monotherapy was superior to placebo after 16 weeks of treatment. Primary endpoints were an IGA score of 0 or 1 and EASI-75 in week 16. Patients achieving an IGA score of 0/1 and/or EASI-75 with tralokinumab in week 16, were randomized again and received tralokinumab Q2W or every 4 weeks or placebo for 36 weeks. In most patients responding to tralokinumab in week 16, the response was maintained with continued tralokinumab treatment also in week 52 without any rescue medication. Given the lack of a head-to-head comparison, network meta-analyses were performed demonstrating a weaker effect of tralokinumab compared to dupilumab for the treatment period of up to 16 weeks.[2]

In phase III trials, the effects in patients responding well to tralokinumab for 16 weeks who continue the treatment as specified, reduce the therapeutic frequency, or discontinue the therapy were examined.

After 16 weeks, patients achieving EASI-75 or IGA success, were again randomized and either continued the treatment every two weeks, were titrated down to every 4 weeks, or received placebo. After 52 weeks, more than 55% of the patients continuing the treatment twice a month still achieved an EASI of 75; the same was true for 50% of the patients treated once a month. More than 51% of the patients continuing the treatment twice a month still had an IGA score of 0 or 1, compared to 39% and 45% of the patients, respectively, changing to treatment once a month.

Dosage: flare, short-term treatment, long-term treatment

The recommended dosage for children and adolescents aged 12 years and above, as well as adults, is 300 mg every 2 weeks after an initial dose of 600 mg at the start of treatment.

Safety

In both phase III trials, adverse events occurred in 76.4% and 61.5%, respectively, of the patients receiving tralokinumab and in 77.0% and 66.0%, respectively, of the patients receiving placebo during the initial phase of 16 weeks.

In particular, tralokinumab resulted less often in ocular complications than dupilumab;[25] a meta-analysis of altogether four published studies calculated 6.2% with tralokinumab compared to 2.1% with placebo.[26]

Combination therapy with TCS, TCI, and UV light is feasible.

Monitoring

According to the current summary of product characteristics, no laboratory or instrumental examinations are required for monitoring the therapy.

Combination with other therapies

In another double-blind phase III trial with placebo, efficacy and safety of tralokinumab in combination with TCS was studied in patients with moderate to severe AD. Compared to placebo, significantly more patients treated with tralokinumab achieved an IGA of 0/1 and an EASI-75 in week 16.[27]

Interval or long-term therapy with Janus kinase (JAK) inhibitors

The treatment of AD with JAK inhibitors is approved for the long-term therapy, *should*, however, be used also as interval therapy in certain disease courses (for example, for predominantly seasonal aggravation).	↑	100% consensus-based
Screening prior to the use of JAK inhibitors and monitoring during treatment *shall* be performed.	↑↑	100% consensus-based
Prior to the use of JAK inhibitors, the individual risk of severe infections *shall* be carefully identified.	↑↑	100% consensus-based
JAK inhibitors *shall not* be used in case of known thromboembolic events or an increased genetic risk of thrombosis.	↓↓	100% consensus-based

The family of Janus kinases (JAK) comprising JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) is a class of cytoplasmic tyrosine kinases[28] binding to the intracellular domain of numerous different cytokine receptor chains to form functional signaling complexes. These regulate the inflammatory process by activation of cytoplasmic transcription factors called *signal transducer and activator of transcription* (STAT). Upon activation, STAT proteins form dimers that migrate into the nucleus and regulate the expression of downstream target genes of inflammatory mediators either positively or negatively. Inhibition of JAK activity may, therefore, be more effective than the targeted inhibition of the signaling pathway of an individual cytokine. Given that the various approved JAK inhibitors inhibit the four JAK to a different degree, the effect of the different JAK is very diverse. Beyond the interruption of the cutaneous proinflammatory cytokine signaling, it was reported that JAK inhibition results in rapid amelioration of chronic pruritus and improves also the function of the skin barrier by upregulating the skin barrier protein filaggrin.[29,30]

Compared to Th2-directed therapies, the broad mode of action also provides an explanation for the broad spectrum of potential adverse effects: inhibition of the antiviral effect of type I interferons results, for example, in an increased incidence of herpes simplex and herpes zoster and an increased susceptibility to infection especially at an advanced age.

In autumn 2022, the EMA re-evaluated all available safety data of all approved JAK inhibitors, the indication for all approved JAK inhibitors for AD or alopecia areata remained unchanged. With the publication of the decision of the European Commission on March 10, 2023, the risk assessment procedure pursuant to article 20 of the Regulation (EC) No. 726/2004 about JAK inhibitors was closed. The warnings and precautions for the use were updated. According to this update and a *Rote-Hand-Brief* (Dear Health Care Provider letter) from March 17, 2023[31], these drugs should be used in the following patients, only if no suitable treatment alternatives are available: patients aged 65 years or above, patients with cardiovascular risk (such as heart attack or stroke), patients currently smoking or former long-term smokers, and patients with enhanced risk of cancer. In patients with risk factors for blood clots in the lung and in deep veins (venous thromboembolism [VTE]) not belonging to the patient groups mentioned above, JAK inhibitors should be used with caution. Moreover, the dosage should be reduced in patient groups at risk of venous thromboembolism, cancer, or severe cardiovascular problems. In addition, regular examinations of the skin are recommended in all patients.[32]

The recommendation strength for therapy with the JAK inhibitors abrocitinib, baricitinib, and upadacitinib,

and the Th2 inhibitors dupilumab and tralokinumab is identical in the German and European guidelines – the selection of the most suitable substance in each individual case shall be made individually for each patient and with the involvement of the patient (*shared decision making*).

Screening prior to the use of JAK inhibitors and monitoring during treatment shall be performed; this is also recommended by the German Society for Rheumatology (DGRh) for rheumatological indications of JAK inhibitors.[33]

Test program before therapy start with JAK inhibitors:

- General status to exclude an active infection
- Verification and, if necessary, booster of the vaccination status
- Hepatitis B screening
- Pregnancy test
- *Test for active or latent tuberculosis*: chest x-ray (not older than 3 months) and suitable screening tests (preferably, *interferon-gamma release assay* [IGRA]). In case of evidence for latent tuberculosis: prophylaxis, if possible, already 4 weeks prior to therapy start, either with isoniazid for altogether 9 months or with rifampicin for altogether 4 months on strict indication and with regular controls.
- *Laboratory analysis*: ESR, CRP, complete blood count, glutamate-oxaloacetic transaminase (GOT), glutamate-pyruvate transaminase (GPT), and creatinine. Lipid status (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides).
  - In patients with an absolute lymphocyte count below 500/μl, an absolute neutrophil count below 1,000/μl, or a hemoglobin level below 8 g/dl, a therapy with JAK inhibitors should not be initiated or should be temporarily interrupted.
  - In clinical studies, the creatine phosphokinase (CPK) level frequently increased on therapy with JAK inhibitors at the start of treatment and remained stable at the higher level even on long-term therapy. In the current summaries of product characteristics of abrocitinib, baricitinib, or upadacitinib, no cases of rhabdomyolysis are mentioned (as of March 2023). While monitoring of CPK is not specified in the rheumatological recommendations for monitoring of the JAK inhibitors baricitinib and upadacitinib due to an absence of clinical relevance, it would be advisable for the indication of AD in, for example, competitive athletes against the background of the short approval time.

Test program during therapy:

- *Clinical examination*: signs of infection, especially of the upper respiratory tract (coughing), as well as herpes zoster, fever, diarrhea, unclear weight loss.
- *Laboratory analysis*: safety and activity parameters (ESR and/or CRP, complete blood count, GOT, GPT) in the first 3 months every 4 weeks, then, in case of stable normal levels, every 8–12 weeks, lipid levels 4–8 weeks after therapy start, then every 6 months.

Potential controls required in addition because of co-medication must be considered.

Abrocitinib

Abrocitinib *shall* be used in adult patients with moderate to severe AD who are candidates for systemic treatment.	↑↑	100% evidence- and consensus-based, see evidence report
The treatment with abrocitinib *shall* be initiated in severe AD after exclusion of contraindications in patients aged up to and including 64 years at the higher dosage approved for this indication. Following response to the therapy, the dosage *shall* be adapted to the clinical disease course.	↑↑	

In the EU, abrocitinib is approved for adults with moderate to severe AD since December 2021. Doses of 100 mg or 200 mg have been approved; in addition, a dose of 50 mg has been approved for the treatment of moderate renal failure and for patients with medication that inhibits cytochrome P450 2c19 or that are weak metabolizers of type 2c19.

Modes of action and efficacy

Like all JAK inhibitors, abroticinib is a drug with a rapid onset of effect. Abrocitinib is a selective oral JAK1 inhibitor that has demonstrated its efficacy in patients with moderate to severe AD as monotherapy (trials MONO-1 and 2) and in combination with topical therapies with respect to response to treatment compared to placebo (trial COMPARE) as measured by IGA and EASI-75 scores. In the MONO trials, the percentage of patients with EASI-75 in week 12 on abroticinib 100 mg (~40–45%) and abrocitinib 200 mg (~61–63%) was markedly higher than with placebo (~10–12%). In the COMPARE trial, the percentage of patients with EASI-75 scores was also significantly higher for abrocitinib 100 mg (~59%) and abrocitinib 200 mg (~70%) compared to placebo (27%).[34] A similar efficacy was demonstrated in the trial JADE-TEEN in adolescents for both the 100 mg and the 200 mg dose in combination with topical therapy.[35] In the COMPARE trial (with dupilumab as comparator arm), higher response rates were observed after 16 weeks of treatment with abrocitinib 200 mg compared to dupilumab in the subgroup with severe disease. The efficacy of abrocitinib 100 mg and dupilumab was similar in this subgroup. In the trial JADE-DARE, efficacy and safety of abrocitinib 200 mg and dupilumab 300 mg were assessed in 727 adult patients. Abrocitinib was significantly more effective in the

time window from 2 to 8 weeks.[36] The results indicate that the probability of response to treatment in patients with severe AD is higher with abrocitinib 200 mg compared to dupilumab in this time window.[36]

Dosage: flare, short-term treatment, long-term treatment

Abrocitinib is approved with daily doses of 100 mg and 200 mg.

In one trial, the renewed response to treatment after flare-up of the disease was analyzed. Of 1,233 patients, 798 responders to the induction therapy (64.7%) were randomized. The probability of a flare during maintenance therapy was 18.9%, 42.6% and 80.9% with abrocitinib 200 mg, abrocitinib 100 mg, and placebo, respectively. Of the patients with flares in the groups treated with abrocitinib 200 mg, abrocitinib 100 mg, and placebo, 36.6%, 58.8%, and 81.6%, respectively, regained an IGA 0/1 score and 55.0%, 74.5%, and 91.8% regained a response according to EASI with *rescue* treatment.[37]

Safety

The following data were obtained from the long-term follow-up of patients from the phase II and phase III trials, as well as a long-term extension study with altogether 2,856 patients (1,614 patient years [PY]) with an exposure of ≥ 24 weeks in 1,248 patients and ≥ 48 weeks in 606 patients (maximum of 108 weeks): in the placebo-controlled cohort (n = 1,540), adverse events (200 mg, 100 mg, placebo), such as nausea (14.6%, 6.1%, 2.0%), headache (7.8%, 5.9%, 3.5%), and acne (4.7%, 1.6%, 0%), occurred in a dose-dependent manner. A dose-dependent transient reduction of the thrombocyte count was observed; 2/2,718 patients (200 mg group) had a confirmed thrombocyte count of $< 50\times10^3/mm^3$ in week 4. The incidence rates (IR) were 2.33/100 PY and 2.65/100 PY for severe infections, 4.34/100 PY and 2.04/100 PY for herpes zoster, and 11.83/100 PY and 8.73/100 PY for herpes simplex in the 200 mg and 100 mg group, respectively.[38]

Although no significant clusters were observed with abrocitinib in clinical trials, the substance should be used with caution in patients with increased risk of deep vein thrombosis or pulmonary embolism, given the potential class effect with other JAK inhibitors (for example, tofacitinib) (see introduction to the substance class).

Combination with other therapies

In trials, abrocitinib has been used in combination with topical anti-inflammatory therapy.

To date, no trials have been published analyzing the use of abroticinib in combination with other systemic therapies.

Specific information

Abrocitinib is a new JAK inhibitor and has not yet been tested in other inflammatory diseases.

Baricitinib

Baricitinib *shall* be used in adult patients with moderate to severe AD who are candidates for systemic treatment.	↑↑	100% evidence- and consensus-based, see evidence report
The treatment with baricitinib *shall* be initiated in severe AD after exclusion of contraindications in patients aged up to and including 64 years at the higher dosage approved for this indication.	↑↑	100% consensus-based
Following response to the therapy, a dose reduction according to the individual benefit-risk assessment and the clinical disease course *may be considered*.	0	
Baricitinib *shall* be used especially in patients with AD who are candidates for systemic treatment and with coexisting alopecia areata or coexisting rheumatoid arthritis.	↑↑	100% consensus-based

Modes of action and efficacy

Like all JAK inhibitors, baricitinib is a drug with a rapid onset of effect. Baricitinib is a selective oral JAK1 and JAK2 inhibitor. The agent was studied in one phase II and several phase III trials in adults with moderate to severe AD at a dosage of 1 mg, 2 mg, and 4 mg once daily compared to placebo. This demonstrated a significant improvement of the EASI score from baseline to week 16, especially at the two higher doses, 2 mg daily (mean difference –5.6 points; 95% confidence interval [CI]: 0.4–10.9 [GRADE assessment: moderate certainty]) and 4 mg daily (mean difference –5.2 points; 95% CI: 0.1–10.4 [GRADE assessment: moderate certainty]).[34] In these trials, a similar efficacy was shown with respect to the IGA score. In theory, the lower JAK selectivity of the JAK1/JAK2 inhibitor baricitinib compared to abrocitinib and upadacitinib may be both favorable (possibly, higher efficacy) and unfavorable due to a broader spectrum of side effects (for example, on JAK2-dependent hematopoiesis). This is, however, not evident from the available data on the safety profile obtained from clinical trials. The concomitant use of TCS was approved in one trial.[39]

Dosage: flare, short-term treatment, long-term treatment

Baricitinib is approved with daily doses of 2 mg and 4 mg.

Currently, data on baricitinib are available for a follow-up period of up to 52 weeks[40] demonstrating long-lasting efficacy. There are no trials available on the treatment of acute flares, and a trial program for pediatric patients is still ongoing.[41] Accordingly, currently no clear dosage recommendations for pediatric patients are available.

Safety

The most common side effects of baricitinib observed in clinical trials include an increase in LDL cholesterol, infections of the upper respiratory tract, acne, and headache. One infection reported in association with baricitinib was herpes simplex. Overall, the incidence of these events identified in a recent combined safety study with 2,531 patients from eight *randomized controlled trials* (RCT) receiving baricitinib over a period of 2,247 patient years (median duration 310 days) was, however, low: eczema herpeticum (n = 11), erysipelas (n = 6), and pneumonia (n = 3). However, patients with a history of recurrent eczema herpeticum and eczema herpeticum in the previous year had been excluded from clinical studies with baricitinib, as well as studies with abrocitinib and upadacitinib. Four opportunistic infections have been reported.[42] Short-term increases of CPK levels are possible, especially after intensive physical activity. During the placebo-controlled period, no malignant diseases, gastrointestinal perforations, confirmed cardiovascular events, or tuberculosis were recorded in patients treated with baricitinib. The incidence of herpes simplex was higher in the 4 mg group (6.1%) compared to the 2 mg group (3.6%) and the placebo group (2.7%). Long-term safety data beyond the period of 16 weeks are currently not available for AD.

Although no significant clusters were observed with baricitinib in clinical trials, the substance should be used with caution in patients with increased risk of deep vein thrombosis or pulmonary embolism, given the potential class effect with other JAK inhibitors (for example, tofacitinib) (see introduction to the substance class).

Combination with other therapies

To date, no studies have been published on the use of baricitinib in combination with other systemic therapies in patients with AD, but the combination therapy of baricitinib with methotrexate is a proven combination regimen for the treatment of rheumatoid arthritis.[43]

Specific information

Patients with AD suffering from inflammatory comorbidities, such as rheumatoid arthritis or alopecia areata, will probably experience positive effects. Baricitinib is already approved for these indications.

Upadacitinib

Upadacitinib *shall* be used in children aged 12 years and above and in adults with moderate to severe AD who are candidates for systemic treatment.	↑↑	100% evidence- and consensus-based, see evidence report
The treatment with upadacitinib *shall* be initiated in severe AD after exclusion of contraindications in the age group from 18 up to and including 64 years at the higher dosage approved for this indication. Following response to the therapy, the dosage *shall* be adapted to the clinical disease course.	↑↑	100% consensus-based
Upadacitinib *shall* be used especially in patients with AD who are candidates for systemic treatment and with coexisting rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, or ankylosing spondylitis.	↑↑	100% consensus-based

Modes of action and efficacy

Like all JAK inhibitors, upadacitinib is a drug with a rapid onset of effect. Upadacitinib is another inhibitor of Janus kinase 1. In one phase II trial with 167 adult patients, three different dosages of upadacitinib (30 mg/day, 15 mg/day, and 7.5 mg/day) were analyzed for the treatment of AD compared to placebo.[44] The trial was conducted for 16 weeks. In all dose groups, upadacitinib was superior to placebo with respect to EASI (mean change [SE] 74% [6.1%] for 30 mg, 62% [6.1%] for 15 mg, 39% [6.2%] for 7.5 mg, and 23% [6.4%] for placebo [$p = 0.03$, < 0.001, < 0.001). Significant improvements were also identified for SCORAD index, numeric rating scale (NRS) for pruritus, and POEM scale. The studies published since then have shown similar efficacy.[45–47] In a trial comparing 30 mg upadacitinib with dupilumab, 247 patients receiving upadacitinib (71.0%) and 210 patients receiving dupilumab (61.1%), achieved EASI-75 ($p = 0.006$).[48] Upadacitinib was also superior to dupilumab with respect to several secondary endpoints including improvement of *Worst Pruritus NRS* already in week 1 (mean [standard error], 31.4% [1.7%] vs. 8.8% [1.8%]; $p < 0.001$), achievement of EASI-75 already in week 2 (152 [43.7%] vs. 60 [17.4%]; $p < 0.001$), and achievement of EASI-100 in week 16 (97 [27.9%] vs. 26 [7.6%]; $p < 0.001$). The superiority of 30 mg upadacitinib was particularly pronounced at the start of therapy. The rates of severe infections, eczema herpeticum, herpes zoster, and laboratory-related adverse events were higher in patients receiving upadacitinib, while the rates of conjunctivitis

and reactions at the injection site were higher in patients receiving dupilumab.

Dosage: flare, short-term treatment, long-term treatment

Upadacitinib is approved with doses of 15 mg and 30 mg.

By now, follow-up observations until week 52 are available showing a similar long-term efficacy and safety profile as the studies over 16 weeks.[49] To date, no trial has assessed the treatment of acute flares, and currently no phase II/III trials in patients under 12 years of age are ongoing.

Safety

In the phase II trial, the cumulative incidence rates for adverse events were 78.6% for 30 mg, 76.2% for 15 mg, 73.8% for 7.5 mg, and 61% for placebo, and similar rates have been observed in the studies published since then.[44] The most common adverse events of upadacitinib were infections of the upper respiratory tract and acne. Other side effects like nausea and headache were particularly pronounced at the start of therapy. The cumulative incidence rates of severe adverse events were 0% for 30 mg, 2.4% for 15 mg, 4.8% for 7.5 mg, and 2.4% for placebo. No drop-out rates were reported.

Although no significant clusters were observed with upadacitinib in clinical trials, the substance should be used with caution in patients with increased risk of deep vein thrombosis or pulmonary embolism, given the potential class effect with other JAK inhibitors (for example, tofacitinib) (see introduction to the substance class).

Combination with other therapies

To date, no studies have been published on the use of upadacitinib in combination with other systemic therapies in patients with AD, but the combination therapy of upadacitinib with methotrexate is a proven combination regimen for the treatment of rheumatoid arthritis.[50]

Specific information

Patients with AD suffering of inflammatory comorbidities, such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and axial spondyloarthritis, or ulcerative colitis, will probably experience positive effects. Upadacitinib is already approved for these indications.

OFF-LABEL THERAPIES

With the approval of new systemic therapeutics, the efficacy of which have been verified by large, high-quality trials, *off-label* treatment is increasingly taking a back seat and should only be considered if approved therapies are exhausted or not feasible.

Azathioprine

Azathioprine *may be considered* for the therapy of chronic severe AD in adulthood, if drugs approved for AD are ineffective or contraindicated (*off-label*).	0	100% evidence- and consensus-based, see evidence report
Azathioprine *shall not* be used in combination with UV therapies.	↓↓	> 50% consensus-based

For background text, see long version

Mycophenolate mofetil

Mycophenolate mofetil/mycophenolic acid *may be considered* in patients with AD who are candidates for systemic treatment, if substances approved for AD are ineffective or contraindicated (*off-label*).	0	100% consensus-based

For background text, see long version

Methotrexate

Methotrexate *should* be used in patients with AD who are candidates for systemic treatment, if substances approved for AD are ineffective or contraindicated (*off-label*).	↑	> 50% evidence- and consensus-based, see evidence report

For background text, see long version

Alitretinoin

Treatment with alitretinoin *should* be performed in adult patients with AD with severe *chronic hand eczema* who are candidates for systemic treatment taking the teratogenicity into account.	↑	100% consensus-based

For background text, see long version

Systemic drugs without recommendations

See long version.

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ACKNOWLEDGMENTS

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

A tabular listing of conflicts of interest of all parties involved can be found in the long version of the guideline.

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How to cite this article: Werfel T, Heratizadeh A, Aberer W, et al. S3 guideline Atopic dermatitis: Part 2 - Systemic treatment. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2023;1-14. https://doi.org/10.1111/ddg.15229