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GUIDELINES

Italian S3-Guideline on the treatment of atopic eczema – First Update, adapted from EuroGuiDerm by the Italian Society of Dermatology and STD (SIDEMAST), the Italian Association of Hospital Dermatologists (ADOI) and the Italian Society of Allergological and Occupational Dermatology (SIDAPA)

Authors of the Italian Adaption of the Euroguiderm Guidelines: Giuseppe ARGENZIANO [1], Francesco CUSANO [2], Monica CORAZZA [3], Salvatore AMATO [4], Paolo AMERIO [5], Luigi NALDI [6], Cataldo PATRUNO [7], Paolo D. PIGATTO [8], Pietro QUAGLINO [9], Paolo GISONDI [10], Andrea CHIRICOZZI [11, 12], Francesco TONON [13], Luca STINGENI [14], Piergiacomo CALZAVARA-PINTON [13] *

[1]Dermatology Unit, University of Campania Luigi Vanvitelli, Naples, Italy, Naples, Italy; [2]Dermatology Unit, G. Rummo Hospital, Benevento, Italy; [3]Section of Dermatology, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [4]Department of Dermatology and STD, ARNAS-Palermo, Palermo, Italy; [5]Section of Dermatology, Department of Medicine and Aging Science, G. D'Annunzio University, Chieti, Italy; [6]Dermatology Unit, San Bortolo Hospital, Vicenza, Italy; [7]Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy; [8]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy; [9]Dermatologic Clinic, Department of Medical Sciences, University of Turin Medical School, Turin, Italy; [10]Dermatology and Venereology Section, Department of Medicine, University of Verona, Verona, Italy; [11]Unit of Dermatology, Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy; [12]Section of Dermatology, Department of Translational Medicine and Surgery, Sacred Heart Catholic University, Rome, Italy; [13]Dermatology Department, University of Brescia, Brescia, Italy; [14]Section of Dermatology, Department of Medicine, University of Perugia, Perugia, Italy

*Corresponding author: Piergiacomo Calzavara-Pinton, Dermatology Department, University of Brescia, Brescia, P.Le Spedali Civili 1, 25123, Brescia, Italy. E-mail: piergiacomo.calzavarapinton@unibs.it

Original authors: Andreas WOLLENBERG [15, 16], Maria KINBERGER [17], Bernd W. ARENTS [18], Nora ASZODI [15], Gabriela L. AVILA VALLE [17], Sebastien BARBAROT [19], Thomas BIEBER [20], Helen A. BROUGH [21, 22], Piergiacomo CALZAVARA-PINTON [13], Stéphanie CHRISTEN-ZÄCH [23], Mette DELEURAN [24], Martin DITTMANN [17], Corinna DRESSLER [17], Antjie H. FINK-WAGNER [25], Nicole FOSSE [26], Krisztián GÁSPÁR [27], Louise A. GERBENS [28], Uwe GIELER [29], Giampiero GIROLOMONI [30], Stamatios GREGORIOU [31], Charlotte G. MORTZ [32], Alexander NAST [17], Uffe NYGAARD [33], Magali REDDING [34], Eva M. REHBINDER [35], Johannes RING [36], Mariateresa ROSSI [37], Esther SERRA-BALDRICH [38], Dagmar SIMON [39], Zsuzsanna Z. SZALAI [40], Jacek C. SZEPIETOWSKI [41], Antonio TORRELO [42], Thomas WERFEL [43], Carsten FLOHR [44, 45]

[15]Department of Dermatology and Allergy, Ludwig Maximilian University, Munich, Germany; [16]Department of Dermatology, Free University of Brussel (VUB), Brussels University Hospital (UZ Brussel), Brussels, Belgium; [17]Division of Evidence-Based Medicine (dEBM), Department of Dermatology, Venereology and Allergology, Charité - Universitätsmedizin Berlin, Berlin, Germany; [18]European Federation of Allergy and Airways Diseases Patients' Associations (EFA), Brussels, Belgium; [19]Department of Dermatology, CHU Nantes, UMR 1280 PhAN, INRAE, Nantes University, Nantes, France; [20]Department of Dermatology and Allergy, University Hospital of Bonn, Bonn, Germany; [21]Children's Allergy Service, Evelina London Children's Hospital, Guy's and St. Thomas' NHS Foundation Trust, London, UK; [22]Paediatric Allergy Group, Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK; [23]University Hospital Lausanne, Lausanne, Switzerland; [24]Aarhus University Hospital, Aarhus, Denmark; [25]Global Allergy and Airways Diseases Patient Platform (GAAPP), Vienna, Austria; [26]Department of Dermatology, University

Hospital Basel, Basel, Switzerland; [27]Department of Dermatology of the University of Debrecen, Debrecen, Hungary; [28]Department of Dermatology, Amsterdam UMC (University Medical Centers), Amsterdam, the Netherlands; [29]Department of Dermatology, University of Giessen, Giessen, Germany; [30]Dermatology and Venereology Section, Department of Medicine, University of Verona, Verona, Italy; [31]Faculty of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [32]Department of Dermatology and Allergy Centre, Odense University Hospital, University of Southern Denmark, Odense, Denmark; [33]Department of Dermato-Venerology, Aarhus University Hospital, Aarhus, Denmark; [34]Eczema Outreach Support, Linlithgow, UK; [35]Dermatology Department, Oslo University Hospital, Oslo, Norway; [36]Department of Dermatology Allergology Biederstein, Technical University Munich, Munich, Germany; [37]Dermatology Unit, Spedali Civili Hospital Brescia, Brescia, Italy; [38]Dermatology, Hospital of Sant Pau, Barcelona, Spain; [39]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [40]Pediatric Dermatology Unit, Heim Pa'l National Children's Institute Budapest, Budapest, Hungary; [41]Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; [42]Hospital Infantil Niño Jesús, Madrid, Spain; [43]Hannover Medical School, Hannover, Germany; [44]St John's Institute of Dermatology, King's College London, London, UK; [45]Guy's and St Thomas' NHS Foundation Trust, London, UK

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ABSTRACT

The evidence- and consensus-based guideline on atopic eczema, published in JEADV on 18 August 2022 (part 1) and 3 September 2022 (part 2) was developed in accordance with the EuroGuiDerm Guideline and Consensus Statement Development Manual. Four consensus conferences were held between December 2020 and July 2021. Twenty-nine experts (including clinicians and patient representatives) from 12 European countries participated. To reflect the most recent evidence on novel systemic medications, an update was published in October 2022. According to the purpose of the Italian Society of Dermatology and STD (SIDEMAST), the Italian Association of Hospital Dermatologists (ADOI) and the Italian Society of Allergological and Environmental Dermatology (SIDAPA) to adapt the EuroGuiDerm guideline on the treatment of atopic eczema into the Italian Healthcare setting, the original update has been supplemented by inserting notes, well highlighted by the original text, to emphasize the laws, rules, procedures and suggestions of the Italian Ministry of Health and regional Health authorities.

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The European guidelines (EuroGuiDerm) on atopic eczema published in JEADV on 18th August 2022 (part 1)[1] and 3rd September 2022 (part 2)[2] were updated in October 2022, to reflect the most recent evidence on novel systemic medications by the European Medicines Agency (EMA) and the UK Medicines and Health care products Regulatory Agency (MHRA): Abrocitinib, an oral selective Janus kinase inhibitor, was approved by the EMA (adults) and MHRA (adults and adolescents). Tralokinumab, a human monoclonal antibody IL-13 inhibitor, received a license for adolescents. In addition, the living network meta-analysis (NMA) 'Systemic Immunomodulatory Treatments for Atopic Dermatitis' by Drucker *et al*.[3] was recently updated, which serves as the evidence base for the systemic treatment section of the European guideline. The guideline development group (GDG) remained almost unchanged and comprised 28 members from 12 countries, including two patient representatives.

For the update, a new recommendation for the use of abrocitinib in patients with atopic eczema who are candidates for systemic treatment was voted on (Figure 1A). This recommendation was accepted unanimously receiving the highest recommendation strength 'we recommend'. Previously, abrocitinib had shown significantly better response on EASI-75 and IGA than placebo in several phase 3 trials of the Atopic Dermatitis Efficacy and

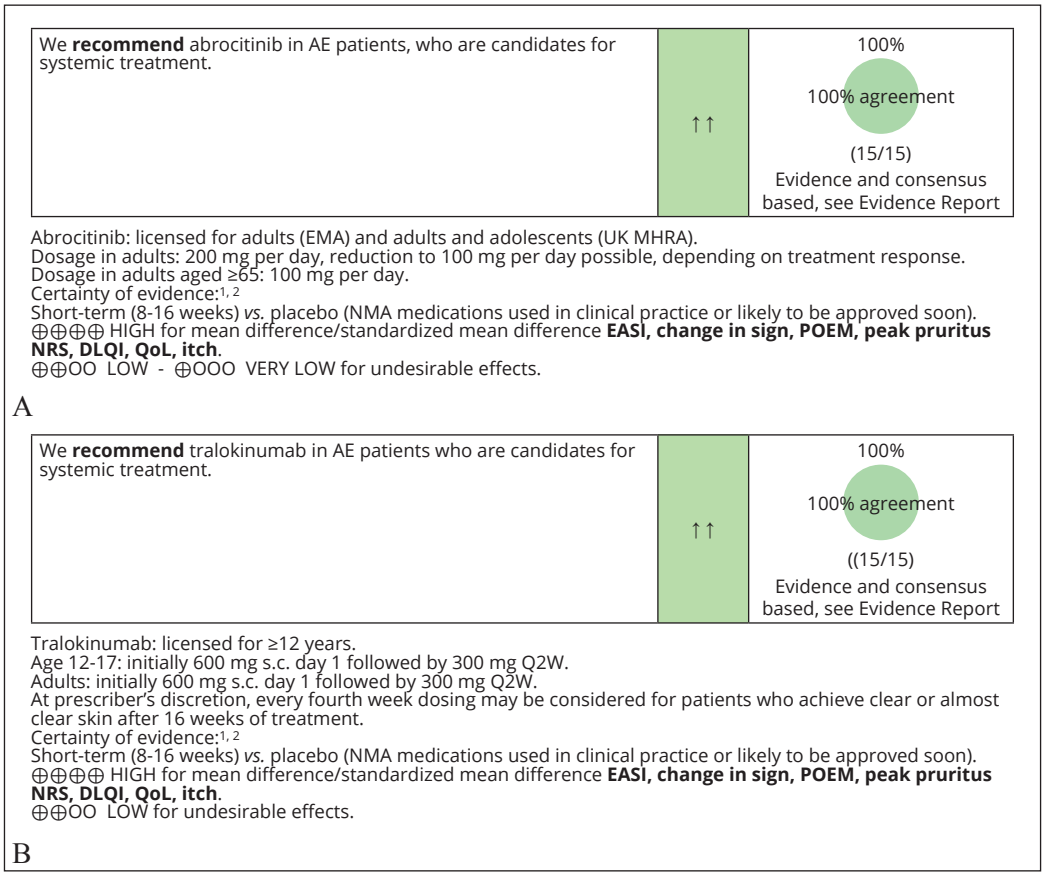

Figure 1.—Recommendations for abrocitinib (A) and for tralokinumab (B).

Safety (JADE) global development program.[4-6] The 200 mg dose of abrocitinib also showed partially better results compared to dupilumab in a recent head-to-head trial.[7] For treatment with abrocitinib, a starting dose of 200 mg once daily is recommended for adults. After a satisfactory response, the dose can be reduced to 100 mg daily. In patients aged 65 years and older, a starting dose of 100 mg once daily is recommended. The same is recommended for adolescents, even if currently licensed only for this age group in the UK. In clinical trials the most common adverse events were nausea, headache, respiratory tract infections and acne. Herpesvirus infections, thrombocytopenia and elevation of serum creatinine phosphokinase occurred only rarely.[8] Because of these potential side effects and based on experience with other Janus kinase inhibitors, the guideline recommends baseline safety screening before starting therapy (full blood count, renal, liver and lipid profile, creatinine phosphokinase level, as well as hepatitis and tuberculosis screening, including a chest radiograph). During therapy with abrocitinib repeat safety investigations (full blood count, renal, liver and lipid profile, and creatinine phosphokinase level) are recommended at four weeks into treatment and then every three months. To minimize the risk of serious side effects, the recently announced recommendations of the EMA's human medicines committee (CHMP) on Janus kinase inhibitors should also be followed.[9]

Abrocitinib

Cibinqo® (Pfizer Inc, New York, NY, USA) is indicated for the treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy. The recommended dose is 100 mg or 200 mg once daily based on individual patient presentation. A dose of 100 mg is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy. For patients ≥65 years of age, the recommended dose is 100 mg once daily. A dose of 200 mg once daily may be appropriate for patients with

high disease burden who are not at higher risk of VTE, MACE and malignancy or patients with an inadequate response to 100 mg once daily. The lowest effective dose to maintain response should be used.
In patients with moderate to severe renal impairment a dose of 50 mg to 100 mg once daily is recommended. The drug is available in the following pharmaceutical forms: 50, 100, 200 mg tablets.

Reimbursement

Abrocitinib (Cibinqo® compresse [15 mg]) is reimbursed in Italy for the treatment of severe atopic dermatitis (EASI ≥24) in adult patients who are candidates for systemic therapy with the clinical indications, limitations and recommendations of all JAK inhibitors (Determina AIFA n. DG/197/2023) available on Gazzetta Ufficiale Serie Generale n.99 del 28-04-2023).

The previous recommendations from the first version of the evidence-based chapter on systemic treatments were re-voted, because new data were available from the updated NMA.[3] However, all existing recommendations in the chapter were confirmed unchanged.

Furthermore, the stepped-care plans for children and adolescents as well as adults were adapted to reflect the new recommendation on abrocitinib and the new lower minimum age for dupilumab (6 months and above).

The stepped-care plan for children and adolescents now also recommends tralokinumab. EMA had previously approved tralokinumab from 12 years of age, as the drug showed significantly better efficacy than placebo in a phase 3 trial in adolescents aged between 12 and 17 years.[10, 11]

For severe atopic eczema in adult patients, six systemic drugs now received the strong recommendation 'we recommend': ciclosporin, the biologics dupilumab and tralokinumab, and the Janus kinase inhibitors abrocitinib, baricitinib and upadacitinib.

Baricitinib

Olumiant® (Eli Lilly and Company, Indianapolis, IN, USA) is approved for the treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy. The recommended dose is 4 mg or 2 mg once daily based on individual patient presentation. A dose of 2 mg is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy. For patients ≥75 years of age, the recommended dose is 2 mg once daily. A dose of 4 mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy or patients with an inadequate response to 2 mg once daily. The lowest effective dose to maintain response should be used.

Reimbursement

Baricitinib (Olumiant® compresse 2 mg and 4 mg) is reimbursed in Italy (Gazzetta Ufficiale Serie Generale n.157 del 07-07-2023) with the same clinical indications, limitations and recommendations reported in the box above for all JAK inhibitors. Baricitinib should be used in combination with topical corticosteroids.

The immunosuppressants azathioprine and methotrexate are used off-label and received the weaker recommendation 'we suggest', reflecting the lower strength of evidence available for the two medications. Systemic corticosteroids were suggested only as rescue therapy in exceptional cases with a weak recommendation strength (Figure 2A).

In children and adolescents, ciclosporin, dupilumab, tralokinumab (Figure 1B) and upadacitinib were strongly recommended for severe atopic eczema. In addition, abrocitinib was also strongly recommended. However, at present this drug has only been approved in the UK for those aged 12 and over. In the EU, this drug can only be used off-label in children and adolescents. As for adults, azathioprine and methotrexate received a weaker recommendation (Figure 2B).

Upadacitinib

Rinvoq® (Abbvie Inc, North Chicago, IL, USA) is approved for the treatment of moderate to severe atopic dermatitis in adults and adolescents aged 12 or older who are candidates for systemic therapy.
The recommended daily doses are 15 mg and 30 mg. A dose of 15 mg is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy. The dose of 30 mg may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy or patients with an inadequate response to 15 mg. The lowest effective dose to maintain response should be used. For adolescents (12-17 years of age) weighing at least 30 kg and for patients ≥65 years of age, the recommended dose is 15 mg once daily.
Upadacitinib should be used in the following patients only if no suitable treatment alternatives are available: those

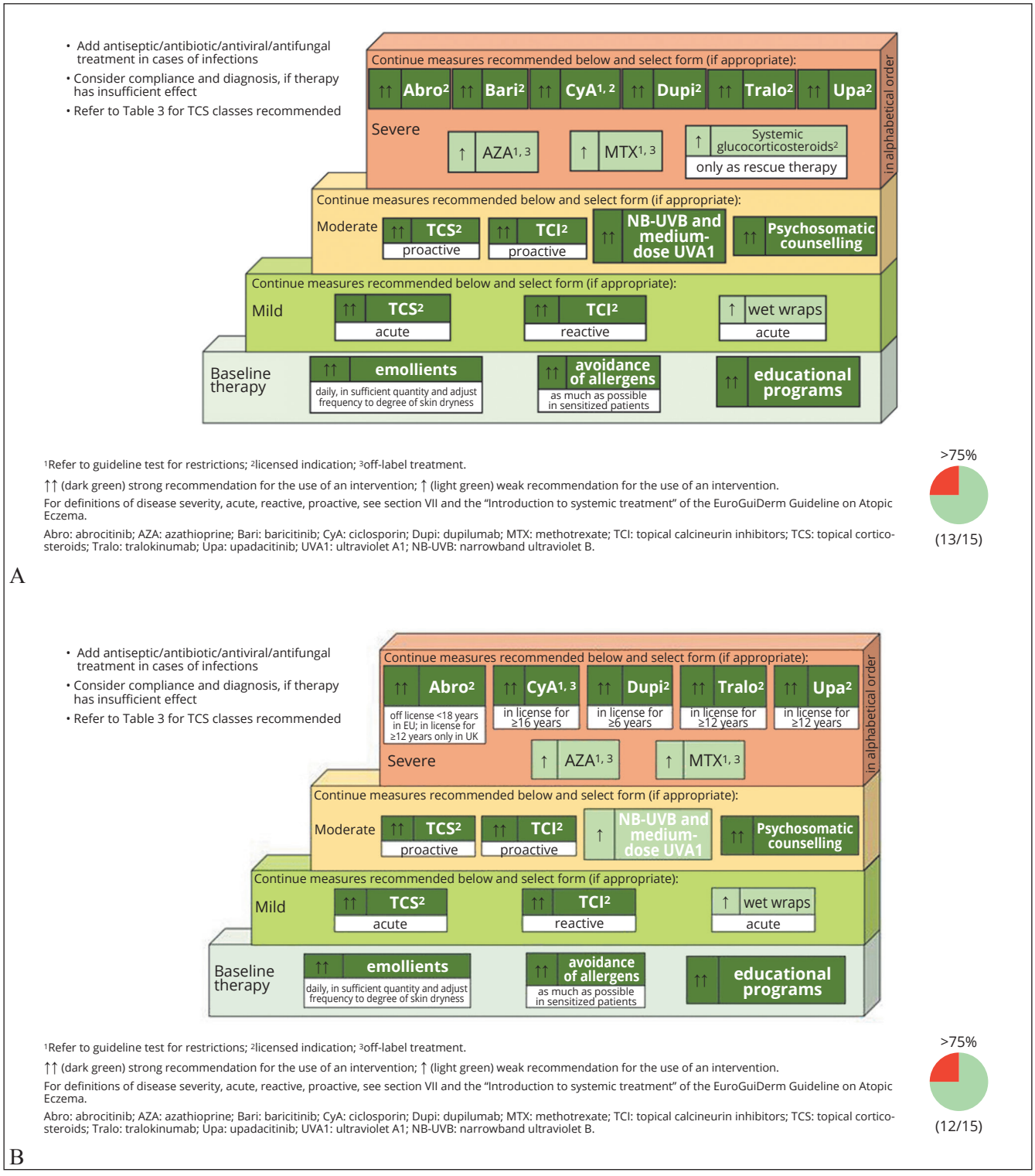

Figure 2.—Stepped-care plans: A) for adults with atopic eczema; B) for children and adolescents with atopic eczema.

aged 65 years or above, those with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers) and those with malignancy risk factors (such as current malignancy or history of malignancy).

Reimbursement

Upadacitinib (Rinvoq® compresse [15 and 30 mg]) is reimbursed in Italy for the treatment of severe atopic dermatitis (EASI ≥24) in adult patients who are candidates for systemic therapy with the clinical indications, limitations and recommendations that are described in the box above for all JAK inhibitors (Determina AIFA n. DG/197/2023) available on Gazzetta Ufficiale Serie Generale n.99 del 28-04-2023).

The steps of baseline therapy and treatments for mild and moderate eczema remain unchanged.

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Conflicts of interest (authors of the Italian Adaption of the Euroguiderm Guidelines)
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Conflicts of interest (original authors)
Sebastien Barbarot received personal fees from Bioderma, Laboratoire La Roche Posay, SanofiGenzyme, AbbVie, Novartis, Janssen, Leo-Pharma, Pfizer, Lilly, UCB, FreseniusKabi, Samsung bioepis, Biogen; Thomas Bieber is/has been lecturer and/or consultant for following companies: AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, Astellas, BioVerSys, Böhringer-Ingelheim, Daichi-Sankyo, Davos Biosciences, Dermavant/Roivant, DS Pharma, Evaxion, FLX Bio, Galapagos/MorphoSys, Galderma, Glenmark, GSK, Incytes, Kymab, LEO, Lilly, L´Oréal, MenloTx, Novartis, Pfizer, Pierre Fabre, Sanofi/Regeneron, UCB; Mette Deleuran declared the participation in advisory boards and/or the activity of speaker for Sanofi-Genzyme, Regeneron, Galapagos, Eli-Lilly, Pfizer, Leo-Pharma, Pierre Fabre Dermocosmetique, Almirall, and AbbVie; Giampiero Girolomoni received personal fees for attending advisory boards or as a speaker at sponsored meetings from Sanofi, Regeneron, Galderma, Almirall, Abbvie, Pfizer, Leo pharma, Novartis, Eli Lilly; Uffe Nygaard received honorary from Sanofi Genzyme A/S for teaching and providing written patient information regarding AE; Johannes Ring received honoraria for lectures from Abbvie and Allergika; Rehbinder Eva Maria received honoraria for lectures from Sanofi Genzyme, Leo Pharma, Novartis, Norwegian Psoriasis and Eczema Association, Norwegian Asthma and Allergy Association; Serra-Baldrich Esther received honorary as speaker, consultant, boards, for Pfizer, Sanofi, Novartis, Lilly, Abbvie, Galderma, Leo; Jacek C. Szepietowski is/has been an Advisory Board Member of Leo Pharma, a speaker for Leo Pharma and SanofiGenzyme and an investigator for Regeneron, Pfizer; Antonio Torrelo received honoraries from Lilly, Sanofi, Pierre Fabre, Pfizer, Abbvie (all advisory boards and/or lectures and/or clinical trials); Thomas Werfel declared advisor and research funding from companies currently active in AE, research: Sanofi, Lilly, Pfizer, LEO, Galderma; Andreas Wollenberg declared honoraries from AbbVie, Lilly, Pierre Fabre, Sanofi, Galderma, L'Oreal, Leo, Novartis.

Authors' contributions
All authors read and approved the final version of the manuscript.

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